A STUDY OF CARDIO PULMONARY MANIFESTATIONS IN SYSTEMIC SCLEROSIS

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CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY OF CARDIO PULMONARY MANIFESTATIONS IN SYSTEMIC SCLEROSIS"** is the bonafide work of **Dr. MATHEW JOSEPH**, in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in April 2012.

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DECLARATION

I, **Dr. MATHEW JOSEPH**, solemnly declare that, I carried out this dissertation "**A STUDY OF CARDIO PULMONARY MANIFESTATIONS IN SYSTEMIC SCLEROSIS**" is a bonafide record of work done by me at the Department of General Medicine, Govt. Rajaji Hospital, Madurai, under the guidance of **Dr. S Vadivelmurugan M.D**, Professor of Medicine, Department of General Medicine, Madurai Medical College, Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of M.D Degree General Medicine Branch-I examination to be held in April 2012.

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CONTENTS

INTRODUCTION

Scleroderma, or systemic sclerosis (SSc), is a chronic multisystem autoimmune disease characterized by a vasculopathy, diffuse fibrosis of skin and various internal organs, and immune abnormalities. The clinical manifestations of this disease are extremely heterogeneous and depend on the presence and degree of various internal organ involvements. It is a profoundly disabling autoimmune disease. The distinguishing pathologic hallmark of SSc is the combination of widespread capillary loss and obliterative vasculopathy of small arteries and arterioles, together with fibrosis in the skin and internal organs. Fibrosis affecting multiple organs distinguishes SSc from other connective tissue diseases. Fibrosis is found in the skin, lungs, gastrointestinal tract, heart, tendon sheath, perifascicular tissue surrounding skeletal muscle, and some endocrine organs. Obliterative vasculopathy as a late finding is prominent in the heart, lungs, kidneys, and intestinal tract. Virtually every organ is affected in SSc. In the previous era scleroderma renal crisis was the most common cause of mortality in these patients. After the advent of ACE inhibitors mortality due to this complication came down. Now the pulmonary and cardiac involvement of scleroderma is the leading cause of death and is present in almost all patients with systemic sclerosis.There is a vast variety of cardiopulmonary involvement in systemic sclerosis.

REVIEW OF LITERATURE

HISTORICAL REVIEW

Cases of skin disease similar to scleroderma may be found in the writings of Hippocrates as far back as 460–370 B.C. Other ancient physicians, including Oribasius (325–403 A.D.) and Paulus Agineta (625–690 A.D.), also wrote on the subject (42). The first detailed description of a scleroderma-like disease was published by Carlo Curzio in Naples in 1753(4). The patient, a young woman suffered from excessive tension and hardness of the skin. Nearly 100 years later, in 1847 Élie Gintrac introduced the term scleroderma, as the skin was the most obvious organ involved(1,5). The word "scleroderma" comes from two Greek words: "sclero" meaning hard, and "derma" meaning skin(43). The extensive involvement of internal organs has only been realized in the second half of the 20th century (6,7,8).

DEFINITION

Systemic sclerosis (SSc) is a connective tissue disorder of unknown etiology, with heterogeneous clinical manifestations, and chronic and often progressive course, which affects the connective tissue of the skin, internal organs and the walls of blood vessels(2,3). It is

characterized by alterations of the microvasculature, disturbances of the immune system and by massive deposition of collagen.

CRITERIA

The American College of Rheumatology (former American Rheumatism Association - ARA) has defined criteria, that are 97 % sensitive and 98 % specific for SSc as follows (10).

Major criterion: Proximal diffuse (truncal) sclerosis (skin tightness, thickening, non-pitting induration)

Minor criteria:

1. Sclerodactyly (only fingers and/or toes)

2. Digital pitting scars or loss of substance of the digital finger pads.

3. Bibasilar pulmonary fibrosis

The patient should fulfill the major criterion or two of the three minor criteria.

CLASSIFICATION

The most accepted and widely used classification is proposed by Le Roy et al and according to them the disease is classified as follows

SSc subsets according to LeRoy at al (11).

1. **Limited Cutaneous SSc**

   Features

- Raynaud's phenomenon for years at presentation
- Skin sclerosis limited to hands, feet, face, and forearms, or absent
- Significant late incidence of pulmonary hypertension, trigeminal neuralgia, calcinosis, and teleangiectasia
- Dilated nailfold capillary loops, usually without capillary dropouts detected by widefield nailfold capillaroscopy.

2. **Diffuse cutaneous SSc**

   Features

- Onset of Raynaud's phenomenon within 1 year of onset of skin changes
- Truncal and acral skin involvement
- Presence of tendon friction rubs
- Early and significant incidence of interstitial lung disease, oliguric renal failure, diffuse gastrointestinal disease, and myocardial involvement
- Presence of anti-DNA topoisomerase I (anti-Scl-70) antibodies
- Absence of anticentromere antibodies
- Nailfold capillary dilatation and destruction detected by widefield nailfold capillaroscopy

EPIDEMIOLOGY

SSc is an acquired sporadic disease with a worldwide distribution and affecting all races. Compared with other connective tissue diseases SSc is relatively rare. The incidence is estimated at 9–19 cases per million per year. Age, gender, and ethnicity are important factors determining disease susceptibility. SSc shows a female predominance that is most pronounced in the childbearing years and declines after menopause. The overall female/male ratio was reported as 4:1(12,13). The most common age of onset for both limited and diffuse cutaneous forms is in the range of 30–50 years.

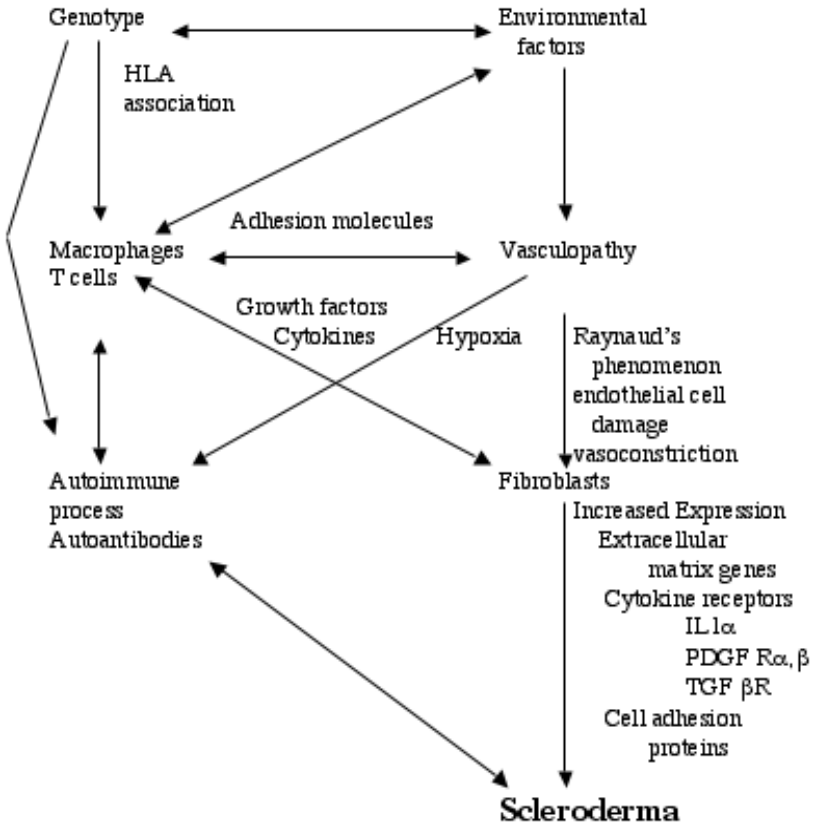
GENETICS

SSc shows a non-Mendelian pattern of inheritance. 1.6% of SSc patients have a first-degree relative with SSc, a prevalence rate substantially higher than in the general population. Genetic investigations in SSc have focused on candidate gene polymorphisms. The genes encoding angiotensin-converting enzyme (ACE); endothelin-1 and nitric oxide synthase; B cell markers (CD19); chemokines (monocyte chemoattractant protein-1) and chemokine receptors; interferon signaling mediators STAT4 and IRF5; migration inhibitory factor; cytokines

[interleukin 1 (IL-1, IL-4, and tumor necrosis factor α (TNF-α)]; growth factors and their receptors [connective tissue growth factor (CTGF) and transforming growth factor β (TGF-β)]; and extracellular matrix proteins [fibronectin, fibrillin, and secreted protein acidic-rich in cysteine (SPARC)] have demonstrated association with the development of systemic sclerosis.

PATHOGENESIS

The three cardinal features of the disease are (1) vasculopathy, (2) cellular and humoral auto immunity, and (3) progressive visceral and vascular fibrosis in multiple organs.



Microangiopathy

Vascular involvement in SSc is extensive, involves multiple vascular beds, and has important clinical consequences. Raynaud's phenomenon, an early manifestation, is characterized by an altered blood-flow response to cold challenge. This initially reversible functional vascular abnormality is associated with alterations in the autonomic and peripheral nervous systems, with impaired production of neuropeptides such as calcitonin gene-related peptide from sensory afferent nerves and heightened sensitivity of α-2-adrenergic receptors on vascular smooth-muscle cells. Raynaud's phenomenon, increased vascular wall thickness, vascular occlusion, devascularization, and thickening of the basement membrane are features which were described many years ago. Changes in the nailfold capillaries are one of the first signs in SSc.(14,15) Furthermore, vascular injury is the basis for the major clinical manifestations of SSc including pulmonary hypertension, myocardial dysfunction and renal involvement. In internal organs, in particular the kidney, arterioles are characterized by intimal proliferation, thinning of the media, and fibrosis of the adventitia, and exhibit accumulation of proteoglycans and collagens(16), probably produced by myofibroblasts . In addition, the vascular pathology is associated with altered vascular

function, with increased vasospasm, reduced vasodilatory capacity, and increased adhesiveness of the blood vessels to platelets and lymphocytes.

Inflammation and Cellular Immunity

In the early stages of SSc, activated T cells and monocytes/macrophages accumulate in lesional skin, lungs, and other affected organs. Infiltrating T cells express CD45 and HLA-DR activation markers and display restricted T cell receptor signatures indicative of oligoclonal expansion in response to (unknown) antigen.

Humoral Autoimmunity

Antinuclear antibodies occur in virtually all patients with SSc. A number of mutually exclusive autoantibodies that is highly specific for SSc have been described. These antibodies show strong association with specific disease phenotypes. Autoantibody levels correlate with disease severity, and titers fluctuate with disease activity. While some SSc-specific autoantibodies are antinuclear and directed against intracellular proteins such as topoisomerase-I, and the RNA polymerases, others are directed against cell-surface antigens or secreted proteins.

Autoantibodies and Associated Features in Systemic Sclerosis (Ssc)

Target Antigen	SSc Subset	Characteristic Clinical Association
Topoisomerase-I	dcSSc	Tendon friction rubs, ILD, cardiac involvement, scleroderma renal crisis
Centromere proteins	lcSSc	Digital ischemia, calcinosis, isolated PAH; renal crisis rare
RNA polymerase III	dcSSc	Extensive skin, tendon friction rubs, renal crisis
U3-RNP	dcSSc	PAH, ILD, scleroderma renal crisis, myositis
Th/T0	lcSSc	ILD, PAH
PM/Scl	lcSSc	Calcinosis, myositis

Fibrosis

Fibrosis affecting multiple organs distinguishes SSc from other connective tissue diseases. Fibrosis characteristically follows, and is thought to be a consequence of, autoimmunity and vascular damage. The process, characterized by progressive replacement of normal tissue architecture with dense connective tissue, accounts for substantial morbidity and mortality. Fibroblasts are mesenchymal cells responsible for maintaining the functional and structural integrity of connective tissue. When activated by TGF-β and related factors, fibroblasts proliferate, migrate, secrete collagens and extracellular matrix, growth

factors, and cytokines, and transdifferentiate into myofibroblasts. The rapid and self-limited physiologic repair program becomes sustained and amplified in pathologic fibrosis, resulting in the irreversible accumulation of scar tissue.

PATHOLOGY

The distinguishing pathologic hallmark of SSc is the combination of widespread capillary loss and obliterative vasculopathy of small arteries and arterioles, together with fibrosis in the skin and internal organs. The vascular lesion is characterized by intimal proliferation in the small and medium-sized arteries, resulting in luminal narrowing. Obliterative vasculopathy as a late finding is prominent in the heart, lungs, kidneys, and intestinal tract. Fibrosis is found in the skin, lungs, gastrointestinal tract, heart, tendon sheath, perifascicular tissue surrounding skeletal muscle, and some endocrine organs. In these tissues, accumulation of connective tissue composed of endothelin-1m collagens, fibronectin, proteoglycans, and other structural macromolecules progressively disrupts normal architecture, resulting in functional impairment of affected organs.

Skin: In the skin, fibrosis causes dermal expansion and obliteration of the hair follicles, sweat glands, and other appendages. Collagen fiber

accumulation is most prominent in the reticular dermis, and the fibrotic process invades the subjacent adipose layer with entrapment of fat cells.

Lungs: Patchy infiltration of the alveolar walls with T lymphocytes, macrophages, and eosinophils occurs in early disease. With progression, interstitial fibrosis and vascular damage dominate. Pulmonary fibrosis is characterized by expansion of the alveolar interstitium, with accumulation of collagen and other connective tissue proteins. The most common histologic pattern in SSc is fibrotic nonspecific interstitial pneumonia.

Gastrointestinal Tract: The lower esophagus is frequently involved, with prominent atrophy of the muscular layers. Replacement of the normal intestinal tract architecture results in diminished peristaltic activity, with gastroesophageal reflux, dysmotility, and small-bowel obstruction. Chronic reflux is associated with esophageal inflammation, ulcerations, and stricture formation and may lead to Barrett's metaplasia.

Kidneys: In the kidneys, lesions in the interlobular and arcuate arteries predominate. Patients with scleroderma renal crisis show dramatic changes in small renal arteries with reduplication of elastic lamina, marked intimal proliferation, and narrowing of the lumen, often accompanied by thrombosis and microangiopathic hemolysis.

Heart: The heart is frequently affected, with prominent involvement of the myocardium and pericardium. The characteristic arteriolar lesions are concentric intimal hypertrophy and luminal narrowing, accompanied by contraction band necrosis reflecting ischemia-reperfusion injury, and patchy myocardial fibrosis that may also affect the conduction system.

CLINICAL FEATURES

Virtually every organ is affected in SSc. While dcSSc is associated with prominent and early internal organ involvement, lcSSc presents with long-standing Raynaud's phenomenon, indolent skin lesions, limited internal organ involvement, and a better prognosis. The initial presentation is quite different in the diffuse and the limited cutaneous forms of the disease.

ORGAN INVOLVEMENT

Raynaud's Phenomenon:

Raynaud's phenomenon is an episodic vasoconstriction in the fingers and toes that occur in virtually every patient with SSc. Vasoconstriction may also affect the tip of the nose and earlobes. Attacks are triggered by exposure to cold, a decrease in temperature, emotional stress, and vibration. Typical attacks start with pallor, followed by cyanosis of variable duration. Eventually erythema develops

spontaneously or with rewarming of the digit. The progression of the three color phases reflects the underlying pathogenic mechanisms of vasoconstriction, ischemia, and reperfusion. It is frequently associated with ischemic lesions and infarction in the digits.

Skin Features:

Early-stage SSc is associated with edematous skin changes. Skin thickening is the hallmark that distinguishes SSc from other connective tissue diseases. The distribution of skin thickening is invariably symmetric and bilateral. It typically starts in the fingers, and then characteristically advances from distal to proximal extremities in an ascending fashion. Hyperpigmentation of the skin also occur. Vitiligo-like hypopigmentation may occur and the pigment loss spares the perifollicular areas, the skin may have a "salt-and-pepper" appearance, most prominently on the scalp, upper back, and chest. Dermal sclerosis and fixed flexion contractures of the fingers may be present. The characteristic facial features are ‘mauskopf’ facies, microstomia, radial furrowing around the mouth, reduced mobility of the eyelids, cheeks & mouth and pinched, beak-like nose. The skin is firmly bound to the subcutaneous fat (tethering) and undergoes thinning and atrophy. Telangiectasiae are prominent on the face, hands, lips, and oral mucosa. Breakdown of atrophic skin leads to chronic ulcerations at the extensor

surfaces of the proximal interphalangeal joints, the volar pads of the fingertips, and bony prominences such as the elbows and malleoli. Healing of ischemic fingertip ulcerations leaves characteristic fixed digital ‘pits’ (stellate scar). Loss of soft tissue at the fingertips due to ischemia is frequent and may be associated with striking resorption of the terminal phalanges (acro-osteolysis). Calcium deposits occur in the skin and soft tissues. Calcinosis cutis is most common in patients with lcSSc who are positive for anticentromere antibodies.

Pulmonary Features:

Pulmonary involvement can be documented in most patients with SSc. There are two main types of significant pulmonary involvement: Intestitial Lung Disease (ILD) and Pulmonary Artery Hypertension (PAH). Less frequent pulmonary manifestations of SSc include aspiration pneumonitis, pulmonary hemorrhage due to endobronchial telangiectasia, obliterative bronchiolitis, pleural reactions, restrictive ventilatory defect due to chest wall fibrosis, spontaneous pneumothorax, and drug-induced lung toxicity. The incidence of lung cancer, particularly bronchioloalveolar carcinoma is more in patients with SSc. The most frequent presenting respiratory symptoms: exertional dyspnea, fatigue, and reduced exercise tolerance are often subtle and slowly progressive. A chronic dry cough may be present. Physical examination may reveal

"Velcro" crackles at the lung bases. Most SSc deaths are now the result of end-stage lung disease (both interstitial and pulmonary vascular).

Upper Gastrointestinal Tract Involvement:

Xerostomia, reduced oral aperture, periodontal disease and resorption of the mandibular condyles are frequent. The frenulum of the tongue may be shortened. Symptoms of gastroesophageal reflux disease (GERD) develop early. Severe erosive esophagitis, esophageal strictures and Barrett's esophagus can occur. Gastroparesis with early satiety, abdominal distention, and aggravated reflux symptoms is common. Gastric antral vascular ectasia (GAVE) in the antrum may occur. These subepithelial lesions, reflecting the diffuse small-vessel vasculopathy of SSc, are described as "watermelon stomach" due to their endoscopic appearance. Patients with GAVE can have recurrent episodes of gastrointestinal bleeding, resulting in chronic unexplained anemia.

Lower Gastrointestinal Tract Involvement:

Impaired intestinal motility may result in malabsorption and chronic diarrhea secondary to bacterial overgrowth. Disturbed intestinal motor function can also cause intestinal pseudoobstruction. Colonic involvement may cause severe constipation, fecal incontinence, gastrointestinal bleeding from telangiectasia, and rectal prolapse. In late-

stage SSc, wide-mouth sacculations or diverticula occur in the colon, occasionally causing perforation and bleeding. An occasional radiologic finding is pneumatosis cystoides intestinalis. Primary biliary cirrhosis may coexist with SSc.

Renal Involvement: Scleroderma Renal Crisis:

Scleroderma renal crisis, the most dreaded complication of SSc, occurs in 10–15% of patients, and almost always within 4 years of the onset of the disease. The pathogenesis involves obliterative vasculopathy and luminal narrowing of the renal arcuate and interlobular arteries. Progressive reduction in renal blood flow, aggravated by vasospasm, leads to juxtaglomerular hyperplasia, increased renin secretion, and activation of angiotensin, with further renal vasoconstriction resulting in a vicious cycle that culminates in malignant hypertension. Palpable tendon friction rubs; pericardial effusion, new unexplained anemia, and thrombocytopenia may be harbingers of impending scleroderma renal crisis. High risk factors for the development of scleroderma renal crisis are male gender, diffuse cutaneous SSc with extensive and progressive skin involvement, and autoantibodies to RNA polymerases I and III.

Cardiac Involvement:

Cardiac disease occurs more frequently in patients with dcSSc than in those with lcSSc, and generally develops within 3 years of the onset of skin thickening. Manifestations include pericardial effusions, atrial and ventricular tachycardias, conduction abnormalities, valvular regurgitation, hypertrophy, and heart failure. Systemic and pulmonary hypertension and lung and renal involvement may also impact on the heart. Despite the presence of widespread obliterative vasculopathy, the frequency of clinical or pathologic epicardial coronary artery disease in SSc is not increased. Clinically evident cardiac involvement in SSc is a poor prognostic factor.

LABORATORY FEATURES

The diagnosis of SSc is made primarily on clinical grounds and is generally straightforward in patients with established disease. Antinuclear autoantibodies are present in almost all patients with SSc. Autoantibodies against topoisomerase-I (Scl-70) and centromere are specific for SSc and are mutually exclusive. Topoisomerase-I antibodies are detected in 31% of patients with dcSSc, but in only 13% of patients with lcSSc; conversely, anticentromere antibodies are detected in 38% of patients with lcSSc, but in only 2% of patients with dcSSc. Anticentromere

antibodies are commonly associated with lcSSc and PAH, and only rarely with cardiac or renal involvement or significant ILD. Anti Topoisomerase-I-positive patients have reduced survival compared to those without this antibody; whereas anti centromere antibody-positive patients have improved survival compared to those without this antibody.

TREATMENT

To date, no therapy has been shown to significantly alter the natural history of SSc. In contrast, multiple interventions are highly effective in alleviating the symptoms and in slowing the progression of the cumulative organ damage. Optimal management incorporates the following principles: prompt and accurate diagnosis; classification and risk stratification based on clinical and laboratory evaluation; early recognition of organ-based complications and assessment of their extent, severity, and likelihood of deterioration; regular monitoring for progression, disease activity, and response to therapy; and continuing patient education.

Disease-Modifying Therapy: Immunosuppressive Agents

Immunosuppressive agents effective in other connective tissue diseases have generally shown modest or no benefit in the treatment of SSc. Glucocorticoids may be useful for alleviating stiffness and aching in

early-stage dcSSc, but do not influence the progression of skin or internal organ involvement. Furthermore, their use in high doses is associated with an increased risk of scleroderma renal crisis. Cyclophosphamide has been evaluated in the treatment of SSc in retrospective and prospective controlled clinical trials. The beneficial effect of cyclophosphamide on lung function wanes upon discontinuation of therapy. In small clinical trials in SSc, methotrexate treatment was associated with a modest improvement in skin scores. Mycophenolate mofetil treatment was associated with improved skin induration in uncontrolled studies and was generally well tolerated. The use of immunomodulatory agents such as cyclosporine, azathioprine, rituximab, extracorporeal photophoresis, imatinib, thalidomide, or rapamycin for the treatment of SSc is currently not well supported by the literature.

Anti-Fibrotic Therapy

D-Penicillamine has been extensively used as an antifibrotic agent. Retrospective studies in SSc indicated that D-penicillamine stabilized and improved skin induration, and prevented new internal organ involvement.

Vascular Therapy

The goal of vascular therapy is to control Raynaud's phenomenon, prevent the development and enhance the healing of ischemic

complications, and slow the progression of obliterative vasculopathy. Patients with Raynaud's phenomenon should dress warmly, minimize cold exposure or stress, and avoid drugs that could precipitate or exacerbate vasospastic episodes. Angiotensin II receptor blockers such as losartan are effective and generally well tolerated. Some patients with Raynaud's phenomenon may require 1-adrenergic receptor blockers (e.g., prazosin), 5-phosphodiesterase inhibitors (e.g., sildenafil), serotonin reuptake inhibitors (e.g., fluoxetine), topical nitroglycerine, and intravenous prostaglandins. Low-dose aspirin and dipyridamole prevent platelet aggregation and may have a role as adjunctive agents. In patients with ischemic finger ulcerations, the endothelin-1 receptor antagonist bosentan reduces the development of new ulcers.

Treatment of Gastrointestinal Complications

Patients with GERD should be instructed to elevate the head of the bed and eat frequent small meals. Proton pump inhibitors reduce acid reflux. vascular ectasia in the gastric antrum (watermelon stomach) is amenable to treatment with laser photocoagulation. Bacterial overgrowth due to small-bowel dysmotility should be treated with short courses of rotating broad-spectrum antibiotics such as metronidazole, erythromycin, and tetracycline.

Treatment of Pulmonary Arterial Hypertension (PAH)

When PAH is symptomatic, treatment should be started with an oral endothelin-1 receptor antagonist or a phosphodiesterase inhibitor such as sildenafil. Patients may also require diuretics, oral anticoagulation, and digoxin when appropriate. Prostacyclin analogues such as epoprostenol or treprostinil can be administered intravenously or by continuous subcutaneous infusion.

Treatment of Renal Crisis

Treatment should be started promptly with short-acting ACE inhibitors, with the goal of achieving rapid normalization of the blood pressure. A majority of patients may need short term or permanent renal replacement therapy. High risk patients with early SSc and extensive and progressive skin involvement should be instructed to monitor their blood pressure daily and report significant alterations immediately. Potentially nephrotoxic drugs should be avoided, and glucocorticoids used only when absolutely necessary, and at low doses.

COURSE

The natural history of SSc is highly variable and difficult to predict. Patient with dcSSc have a more rapidly progressive disease and worse prognosis than those with lcSSc.

PROGNOSIS

SSc confers a substantial increase in the risk of premature death, with age- and gender-adjusted mortality rates that are fivefold to eightfold higher compare to the general population. In one population-based study of SSc patients with all forms of the disease, the median survival was 11 years. In patients with dcSSc, 5- and 10-year survivals are 70% and 55%, respectively, whereas in patients with lcSSc, 5- and 10-year survivals are 90% and 75%, respectively.

PULMONARY AND CARDIAC MANIFESTATIONS OF SYSTEMIC SCLEROSIS

Interstitial Lung Disease (ILD):

Although ~90% of SSc patients have been found to have pulmonary interstitial fibrotic changes at postmortem examination or on high-resolution computed tomography (HRCT) of the chest, only ~40% develop moderate or severe restrictive pulmonary disease on physiologic pulmonary function testing (forced vital capacity [FVC] of ≤75% of predicted)[17]. ILD and pulmonary fibrosis cause restrictive pulmonary function defect with impaired gas exchange, characterized on PFT by decreased FVC and DLCO but unaffected flow rates. Clinically significant ILD develops in 16–43% of patients with SSc. Risk factors

include male gender, African American race, diffuse skin involvement, severe gastroesophageal reflux, and the presence of topoisomerase-I autoantibodies, as well as a low FVC or DLCO at initial presentation. In patients who develop significant ILD, the most rapid progression in lung disease occurs early in the course of the disease (within the first 3 years), when the FVC can decline by 30% per year. The histologic pattern on lung biopsy may be helpful in predicting the risk of progression of ILD. The most common pattern in SSc, nonspecific interstitial pneumnia, carries a better prognosis than usual interstitial pneumonia. The earliest interstitial changes in SSc interstitial lung disease (ILD) occur in the subpleural areas in the posterior bases of both lungs (17).

ETIOPATHOGENESIS:

Although it is clear that ILD in SSc is associated with interstitial and alveolar inflammation, pulmonary vascular abnormalities and interstitial fibrosis, it is not clear which, if any, are the primary events. It may well be that there is another as yet unidentified process which, once initiated, leads to all these downstream events. There are strong suggestions, however, that inflammation (seen on lung biopsy or in the bronchoalveolar lavage [BAL] fluid) is an early process and that when present, it predicts progressive decline in physiologic lung function measured primarily as %FVC). Although long felt to be the result of a

bland fibrosing process, the “alveolitis” associated with SSc lung disease is now known to be associated with an active, inflammatory process that culminates in fibrosis and significant alteration of the pulmonary microarchitecture. Numerous studies have confirmed the presence of pro-inflammatory and profibrotic cytokines in the BAL fluid obtained from SSc patients with ILD. For example, levels of the chemokine IL-8 are elevated, perhaps contributing to the neutrophilic alveolitis characteristic of SSc ILD. Tumor necrosis factor-alpha (TNF-alpha) levels are also elevated (in serum and BAL fluid) and have been shown to correlate inversely with FVC. Potent fibroblast mitogens (eg, platelet-derived growth factor [PDGF] and thrombin) and profibrotic factors (eg, transforming growth factor-beta [TGF-beta] and connective tissue growth factor [CTGF]) are elevated in SSc BAL fluid and may play a role in the pathogenesis of ILD in SSc.

SYMPTOMS:

Dyspnea is the most common complaint of patients with ILD and when severe is a most debilitating symptom. With mild degrees of ILD, the dyspnea usually becomes apparent only with exertion. By the time dyspnea is occurring at rest, it is usually a sign that the lung disease is moderate or severe (either from ILD or from pulmonary vascular disease). Cough is another common symptom of lung fibrosis. Usually,

the cough is nonproductive and made worse by exertion. A productive cough, or hemoptysis, requires further evaluation to rule out such conditions as aspiration pneumonia or neoplasm.

INVESTIGATIONS:

Pulmonary Function Testing

Pulmonary function testing is a valuable tool for evaluating the respiratory system. Insight into underlying pathophysiology can often be gained by comparing the measured values for pulmonary function tests obtained on a patient at any particular point with normative values derived from population studies. The percentage of predicted normal is used to grade the severity of the abnormality. PFTs can include simple screening spirometry, formal lung volume measurement, diffusing capacity for carbon monoxide, and arterial blood gases. Pulmonary function studies measure and record the properties of four lung components. These include the airways (large and small), lung parenchyma (alveoli, interstitium), pulmonary vasculature, and the bellows-pump mechanisms.

Spirometry:

Spirometry is the most commonly used lung function screening study. A spirogram is a graphic representation of bulk air movement

depicted as a volume-time tracing or as a flow-volume tracing. Values generated from a simple spirogram provide important graphic and numeric data regarding the mechanical properties of the lungs, including airflow (forced expiratory volume in 1 second [FEV_1]) and exhaled lung volume (FVC). The most common parameters measured in Spirometry are Vital capacity (VC), Forced vital capacity (FVC), Forced expiratory volume (FEV) at timed intervals of 0.5, 1.0 (FEV1), 2.0, and 3.0 seconds, Forced expiratory flow 25–75% (FEF 25–75) and Maximal voluntary ventilation (MVV). Results are usually given in both raw data (litres, litres per second) and percent predicted - the test result as a percent of the "predicted values" for the patients of similar characteristics (height, age, sex, race and weight). The interpretation of the results can vary depending on the physician and the source of the predicted values. Generally speaking, results nearest to 100% predicted are the most normal and results over 80% are often considered normal[18].

Forced Expiratory Volume in one Second (FEV1):

The FEV_1 is the most widely used parameter to measure the mechanical properties of the lungs. In normal persons, the FEV_1 accounts for the greatest part of the exhaled volume from a spirometric maneuver and reflect mechanical properties of the large and the medium-sized airways. In a normal flow-volume loop, the FEV_1 occurs at about 75% to

85% of the FVC. This parameter is reduced in obstructive and restrictive disorders.

Forced Vital Capacity

FVC is a measure of lung volume and is usually reduced in diseases that cause the lungs to be smaller. Such processes are generally termed restrictive and can include disorders of the lung parenchyma, such as pulmonary fibrosis, or of the bellows, including kyphoscoliosis, neuromuscular disease, and pleural effusion. However, a reduction in FVC is not always due to reduced total volumes and can occur in the setting of large lungs hyperinflated due to severe airflow obstruction and air trapping, as in emphysema. This phenomenon referred to as pseudo restriction. Reduced FVC can occur despite a normal or increased total lung volume (19).

FEV1/FVC ratio (FEV1%)

In healthy adults this should be approximately 75–80%. In obstructive diseases (asthma, COPD, chronic bronchitis, emphysema) FEV_1 is diminished because of increased airway resistance to expiratory flow and the FVC may be decreased (for instance by premature closure of airway in expiration). This generates a reduced value (<80%, often ~45%). In restrictive diseases (such as pulmonary fibrosis) the FEV_1 and

FVC are both reduced proportionally and the value may be normal or even increased as a result of decreased lung compliance.

MEASUREMENT	OBSTRUCTIVE PATTERN	RESTRICTIVE PATTERN
FVC	Reduced or normal	reduced
FEV1	reduced	normal or reduced
FEV1/FVC	reduced	normal or increased
TLC	normal or increased	reduced

Diffusing Capacity

Spirometry and lung volumes elucidate the mechanics of ventilation but do not address the gas-transfer function of the lung. With use of a highly diffusable gas (carbon monoxide [CO]) as a surrogate for oxygen, the diffusing capacity of lung for CO (DLCO) estimates the patient's ability to absorb alveolar gases. Diffusion in the lungs is most efficient when the surface area for gas transfer is high and the blood is readily able to accept the gas being transferred. It is thus decreased in:

• Conditions that minimize the ability of the blood to accept and bind the gas that is diffusing (eg, anemia)

• Conditions that decrease the surface area of the alveolar-capillary membrane (eg, emphysema, pulmonary embolism)

• To a smaller degree, conditions that alter the membrane's permeability or increase its thickness (eg, pulmonary fibrosis).

Conversely, conditions resulting in an increased effective pulmonary blood volume cause an elevated DLCO.

The most frequently abnormal PFT in SSc is the DLCO. Unfortunately this test can reflect damage from a multitude of processes, including obstructive, restrictive, and pulmonary vascular involvement. Fortunately in SSc, obstructive disease is not all that common, and as a result, a reduced DLCO usually reflects restrictive and/or pulmonary vascular disease. FVC on the other hand is a better measure of ILD or restrictive lung disease, assuming confounding issues with poor patient effort or weak respiratory muscles can be ruled out.

Chest Radiography: The chest radiograph may be normal in patients with early fibrosis. In late stages, chest radiograph shows changes identical to that of Interstitial Pulmonary Fibrosis (IPF). Chest radiographs typically show a fine reticular or reticulonodular pattern involving the lower lung zones in early stages. With progression of disease, the reticular pattern becomes more coarse and diffuse, and honeycombing may be seen .It is useful in detecting clinically significant pleural effusion

High resolution computed tomography:

The use of cross sectional images in CT makes it possible to distinguish between densities and provide accurate size assessment of lesions. With high resolution CT, the thickness of individual cross sectional images is approximately 1 to 2 mm rather than the usual 10 mm and the images are reconstructed with high spatial resolution algorithms.

Chest HRCT is a tool that is much more sensitive in showing interstitial changes than is standard chest radiography. The hope is that it will also be a tool sensitive enough to find early inflammatory changes that will predict outcome (much as BAL). Groundglass (GG) opacification (a hazy-appearing opacification through which normal lung architecture can be seen) may be such a sign of inflammation, particularly if there is little or no obvious fibrotic change in the same area. It is likely that HRCT scans may replace BAL as a method to evaluate ILD in SSc patients. The advantages of HRCT scans include the noninvasive nature of the study, which facilitates serial studies over time, as well as the fact that with HRCT both lungs can be examined in their entirety.

Broncho Alveolar Lavage:

The Bronchoscope can be used to sample material from the distal pulmonary parenchyma. The upper airway is anaesthetized and the

bronchoscope is introduced and wedged into a subsegmental airway. Aliquots of sterile saline are introduced through the scope. This allows sampling of the cells and organisms from the alveolar spaces. The lavage is filtered and the cells are stained with Papanicolaou's method and differential count is performed.

The definitions of alveolitis that best predict declines in FVC and DLCO in SSc relate primarily to increases in polymorphonuclear (PMN) and eosinophilic (EOS) leukocytes in BAL fluid. One common definition of alveolitis includes the presence of ≥3% PMN and/or ≥2% EOS leukocytes in the BAL fluid. Although lymphocytosis (≥20% of BAL cells) may accompany increased %PMN and %EOS leukocytes, it is less clear what the presence of an isolated lymphocytosis means with regard to future lung function or therapy in SSc. Using definitions similar to the one listed above, several studies have shown that the presence of increased PMN and/or EOS leukocytes in BAL fluid predicts continued loss of FVC and DLCO.

Open Lung Biopsy:

The "gold standard" for the evaluation of restrictive lung disease is the open lung biopsy that can show the type and degree of inflammation as well as the degree of fibrosis. It can also show the presence of other

processes that may mimic or confound SSc ILD (ie, sarcoidosis, bronchiolitis obliterans with organizing pneumonia [BOOP], aspiration from gastroesophageal reflux). The predominant lesion in SSc is nonspecific interstitial pneumonitis (NSIP). Because the test is invasive, is associated with significant morbidity even if done thorascopically, can give differing results depending on what area(s) are selected for biopsy, and may not provide accurate prognostic or therapeutic guidance, it is not considered the test of choice.

DIFFERENTIAL DIAGNOSIS

Pulmonary vascular involvement with pulmonary hypertension and cardiomyopathy with diastolic dysfunction can occur in isolation or concurrently with ILD and produces symptoms similar to ILD. Occult GERD may present with atypical symptoms, such as cough, asthma-like respiratory complaints, wheezing, pneumonia, or hoarseness (symptoms not usually associated with GERD). Because occult GERD is so common, it must always be considered to be part of the problem in patients with respiratory complaints and should be treated aggressively with antireflux measures. Pulmonary infection (often the result of occult or overt reflux with mini-aspirations) may also confound the evaluation and management of ILD and should be considered in all SSc patients who report increased dyspnea and cough, especially if the cough is productive.

PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension (PAH) is the leading cause of death in patients with systemic sclerosis (SSc) with limited scleroderma and increasingly recognized as a cause of pulmonary morbidity in diffuse scleroderma as well. PAH can occur in the absence of interstitial lung disease, most typically in patients with SSc with limited scleroderma, or as a reflection of both vascular and microvascular injury in the setting of diffuse scleroderma. PAH is a progressive disease characterized by increased pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), ultimately producing right heart failure and death. Of all CTDs, PAH is most often seen in SSc.

Definition

PAH is defined as a mean pulmonary artery pressure (PAP) of >25 mm Hg at rest, or >30 mm Hg during exercise, the absence of an elevated pulmonary capillary wedge pressure or left ventricular end diastolic pressure (ie, <15 mm Hg) and a pulmonary vascular resistance >3 U • M^2.

PATHOPHYSIOLOGY AND NATURAL HISTORY

Regardless of etiology, PAH is characterized by pulmonary vascular smooth muscle hypertrophy, intimal fibrosis, and in situ thrombosis. Recent evidence suggests endothelial dysfunction is

important in its pathobiology. PAH is a very significant pulmonary complication in SSc. One series reported that 33% to 63% of pulmonary-related deaths in patients with SSc were due to PAH. Others have observed that patients with isolated PAH had a 2-year survival rate of 40% compared with 88% of SSc patients without PAH.

DIAGNOSIS

Slowly progressive exertional dyspnea is the most common symptom of PAH. The diagnosis of PAH is a process of exclusion. In the absence of other causes, dyspnea should prompt evaluation for PAH in SSc patients, particularly those with lcSSc. Diagnostic testing of patients suspected of having PAH should begin with noninvasive tests to identify potential underlying diseases and rule out alternative diagnoses. These tests include electrocardiography, echocardiography, pulmonary function tests, chest radiography, ventilation-perfusion lung scan, and high resolution CT. In patients in whom noninvasive tests suggest PAH, right heart catheterization is necessary to confirm the diagnosis.

2-D Echocardiography with Doppler Interrogation

Echocardiography can reveal typical features observed in patients with PAH: enlarged right heart chambers, right ventricular hypertrophy, abnormal interventricular septal position, and a normal to small left

ventricle. With Doppler interrogation, the right ventricular systolic pressure, which is equal to the pulmonary arterial systolic pressure in the absence of pulmonary stenosis, can be estimated by the velocity of the tricuspid regurgitation jet.

Ventilation-Perfusion Lung Scan

For patients suspected of having isolated PAH, chronic thromboembolic disease must be ruled out. If a ventilation-perfusion (V/Q) lung scan is read as high probability or indeterminate probability, pulmonary angiography is needed to rule out chronic thromboembolic disease. In patients with suspected chronic thromboembolic disease, multiple larger perfusion defects occur.

Right Heart Catheterization

Right heart catheterization is necessary to confirm the diagnosis of PAH. The importance of right heart catheterization, when echocardiography suggests PAH, is that pulmonary artery pressure measurements obtained by right heart catheterization are not estimations as they are with echocardiography. Furthermore, left sided heart disease, a frequent cause of elevated pulmonary artery pressure ie, PCWP or LVEDP > 15 mm Hg, can be ruled out only by right heart catheterization.

AIMS AND OBJECTIVES

1) To study the pulmonary and cardiac manifestations of systemic sclerosis.

MATERIALS AND METHODS

Place of study	:	Department of Medicine. Govt. Rajaji Hospital, Madurai
Design	:	Cross Sectional Study.
Period of study	:	One year.
Ethical approval	:	Obtained from Institutional Ethical Committee, headed by Dean, Govt. Rajaji Hospital.
Consent	:	Informed consent obtained from all patients.
Financial Support	:	Nil
Conflict of Interest:		Nil
Statistical software:		EPI Info 2008.
Study population	:	Patients attending Rheumatology OP, Dermatology OP, General Medicine OP & Thoracic Medicine OP with Systemic Sclerosis

Inclusion criteria:

1) Patients who satisfied American College of Rheumatology criteria 1980 for the diagnosis of Systemic Sclerosis, irrespective of age, sex and duration of disease.

Exclusion criteria:

1) Previous history of Bronchial asthma/ Chronic Obstructive Airway Disease.
2) Patients with respiratory infections, including pulmonary tuberculosis.
3) Previous history of pulmonary tuberculosis.
4) Patients who are smokers.
5) Patients with occupation prone to develop occupational lung disease.
6) Those who have disorder like SLE, Rheumatoid Arthritis, MCTD and overlap syndromes.
7) Patients with coronary artery disease, rheumatic heart disease or congenital heart disease.

Thirty two patients attending Rheumatology OP, Dermatology OP, Thoracic Medicine OP or General Medicine OP and the corresponding wards, Govt. Rajaji Hospital, Madurai, who were diagnosed to have Systemic Sclerosis, were selected for the study.

The selected patients were evaluated with detailed history regarding the duration of disease, symptoms, relevant past history, habits and occupation.

A detailed dermatological examination which includes type and extension of skin thickening was done and the Modified Rodnan Skin Score was calculated. Other dermatological manifestations like sclerodactily, pitted scar on the pulp of fingers, hyper pigmentation, telangectasia, salt & pepper lesions, skin ulcers, calcinosis cutis, microstomia and flexion contractures of the fingers also noted. A detailed respiratory system examination with particular emphasis to the presence of pleural effusion, Velcro crackles and wheeze conducted. Cardiovascular system of the patient is also examined in detail.

Hemoglobin, White blood cell count, Differential count, ESR, Blood Urea, Serum Creatinine, Blood sugar, ECG, Chest X ray were done for all patients. The antibody profile of the patients which include ANA, anti ds DNA, Scl 70 antibody and anti centromere antibody was also done.

After assessing baseline clinical and laboratory parameters, all patients were subjected to spirometric evaluation, High Resolution Computerized Tomography (HRCT), and ECHO Cardiogram.

The Spirometry was performed using Knudsen's computerized Spirometer. All the Spirometric parameters were expressed as percentage of predicted value for that particular age, sex, height, and weight comparable to South Indian population defined by Knudsen et al.

The entire test was repeated on three occasions and the best of the three readings were taken. Among the various spirometric parameters, the following were analyzed.

1. Forced Vital Capacity (FVC).
2. Forced Expiratory Volume in first second (FEV1).
3. Percentage of FVC expelled as FEV1 (FEV1/FVC)

All the patients were subjected to HRCT after getting informed consent. Serial slices 2 mm in width and 10 mm apart were taken from the apex of the lung to base and reconstructed on a High-resolution bone algorithm. HRCT was done from the Department of Radiology, Govt. Rajaji Hospital, Madurai. Reports were given by qualified Radiologists.

ECHO cardiogram was done at the Department of Cardiology, Govt. Rajaji Hospital, Madurai with ALOKA ProSound 4000 machine.

The information collected regarding all the selected cases were recorded in a master chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2008). Using the software range, frequencies, percentage, mean, standard deviation and p value were calculated. P value of < 0.05 was taken as significant.

RESULTS AND ANALYSIS OF OBSERVED DATA

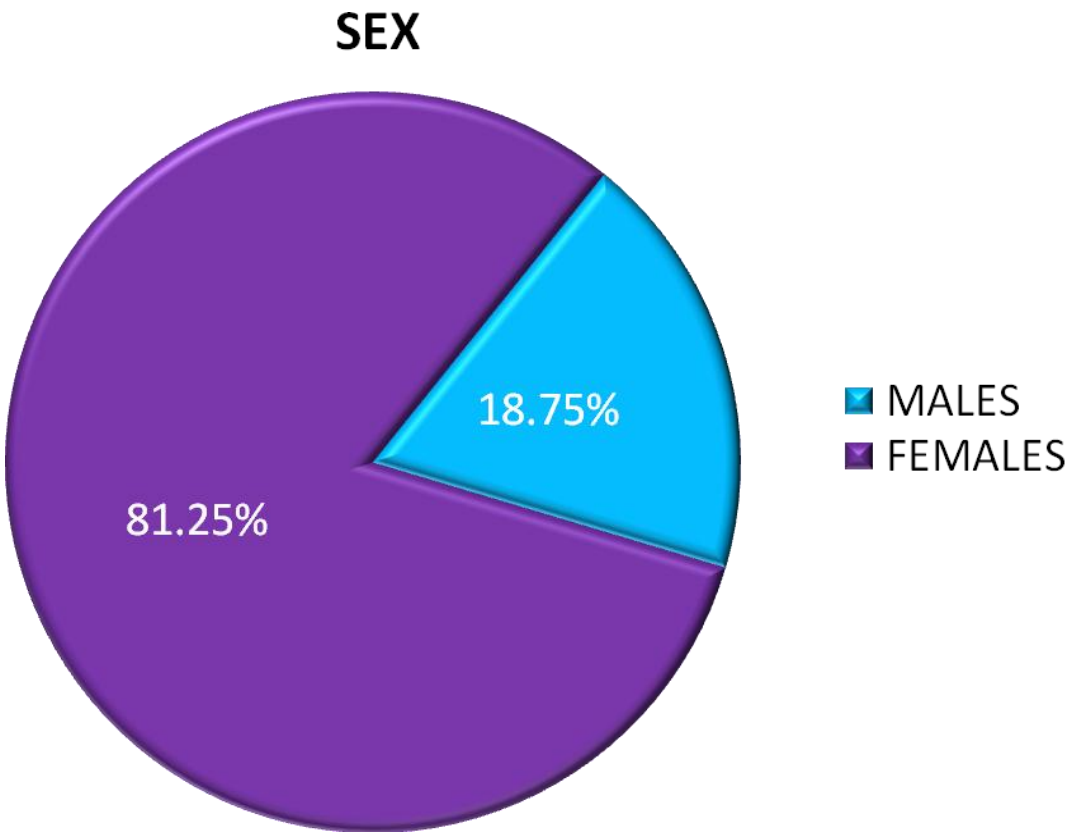
TABLE 1. SEX DISTRIBUTION AMONG PATIENTS:

Sex	No. of Patients	%
Male	6	18.75%
Female	26	81.25%
Total	32	100%

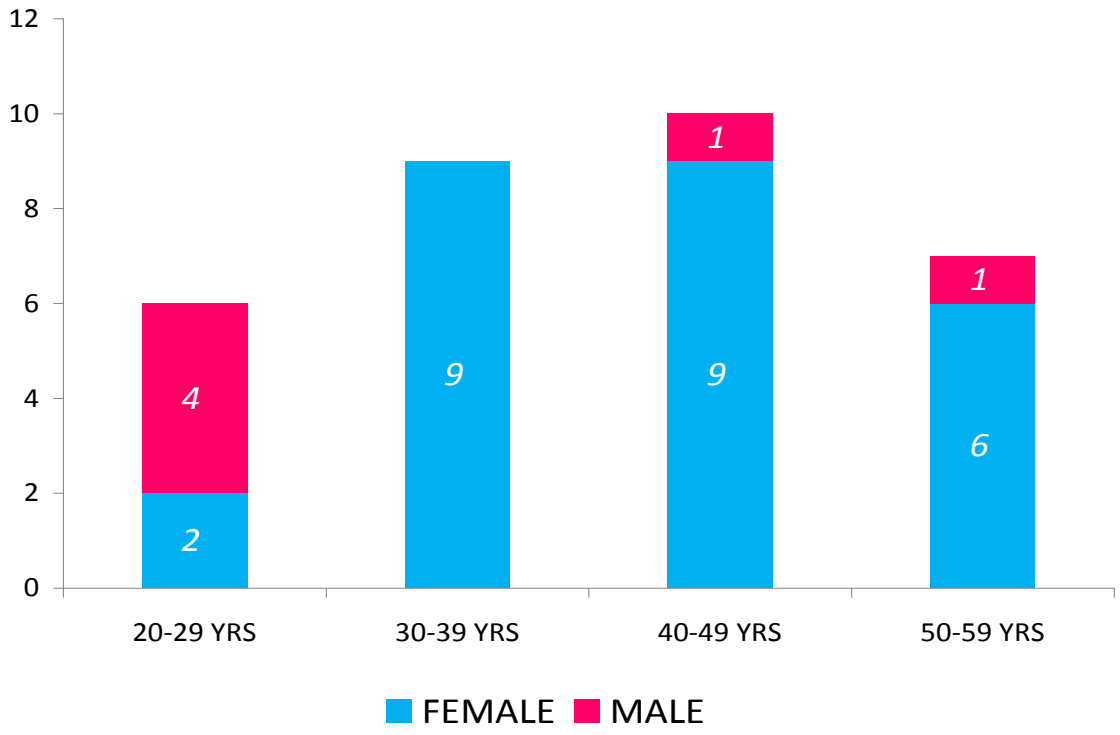
In this study out of 32 patients, 26 are females and the rest 6 are males. ie 81.25% are females and 18.75% are males. The male to female ratio is 1:4.33

TABLE 2 : AGE DISTRIBUTION OF PATIENTS

Age group	Female	Male	Total No.	%
20 – 29 yrs	2	4	6	18.75%
30 - 39 yrs	9	0	9	28.12%
40 - 49 yrs	9	1	10	31.25%
50 – 59 yrs	6	1	7	21.88%
TOTAL	26	6	32	100%


SEX
18.75%
81.25%
MALES
FEMALES

AGE DISTRIBUTION OF PATIENTS IN NO.



The age of the patient ranges between 20 years and 58 years. The average age of the patients is 39.28 years. Most patients come under the age group 40-49 years.

TABLE 3: DURATION OF SYMPTOMS:

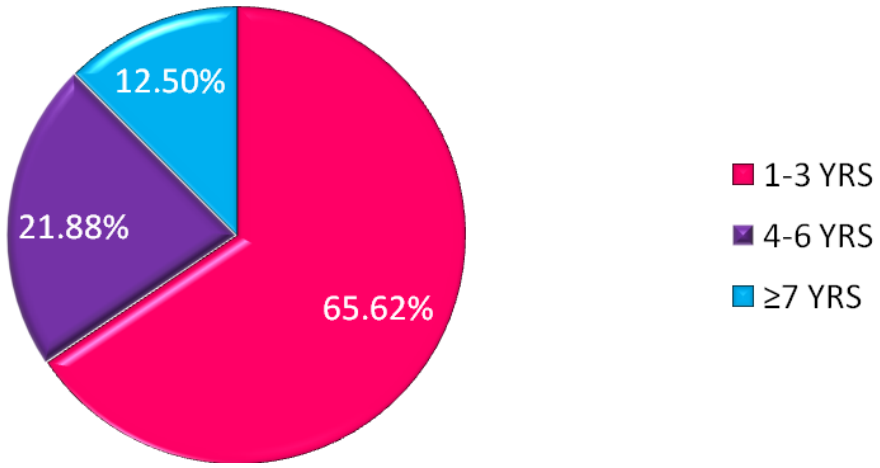
Duration of symptoms	No. of patients	%
1 – 3 years	21	65.62%
4 – 6 years	7	21.88%
≥7 years	4	12.5%
TOTAL	32	100%

65.62% patients had the symptoms for a period of 1-3 years. The mean duration is 3.16 years.

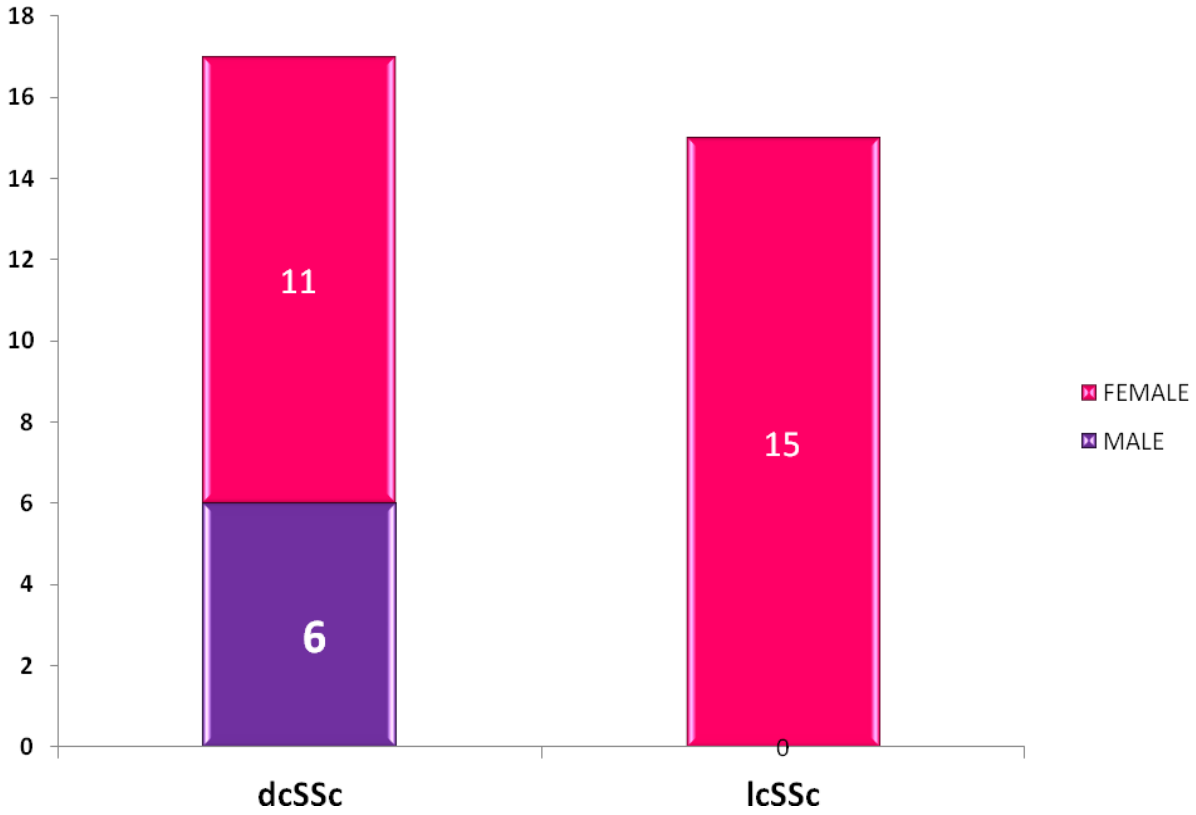
TABLE 4: DISEASE SUBTYPES

	MALE	%	FEMALE	%	TOTAL	%
dcSSc	6	100	11	42.31%	17	53.12%
lcSSc	0	0	15	57.69%	15	46.88%
TOTAL	6	100	26	100%	32	100%

DURATION OF DISEASE



DISEASE SUBTYPES: NO. OF PATIENTS



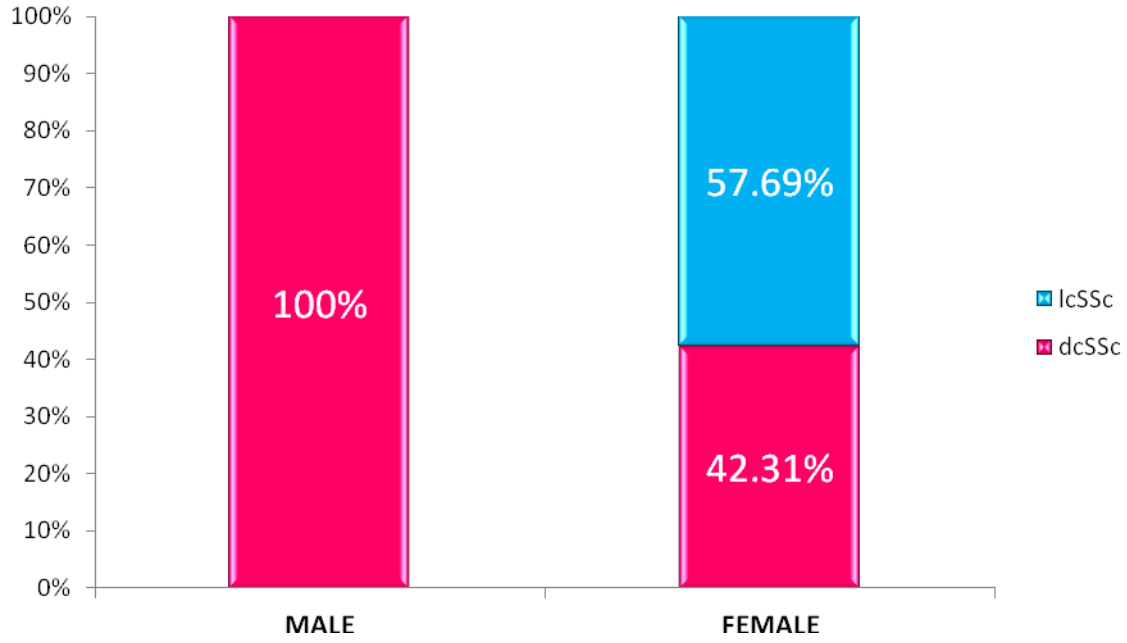
53.12% of the study population had diffuse cutaneous systemic sclerosis and the rest 46.88% had limited cutaneous systemic sclerosis. All the male patients had diffuse cutaneous systemic sclerosis and nobody comes under limited cutaneous subset. Among female patients 57.69% had limited cutaneous systemic sclerosis and the rest 42.31% had diffuse cutaneous systemic sclerosis.

TABLE 5: PRSENCE OF RAYNAUD'S PHENOMENON

	RAYNAUD'S PRESENT		RAYNAUD'S ABSENT		TOTAL	
	NO.	%	NO.	%	NO.	%
dcSSc	9	52.94%	8	47.06%	17	100%
lcSSc	11	73.33%	4	26.67%	15	100%

52.94% of the patients with diffuse cutaneous systemic sclerosis had Raynaud's phenomenon. Among patients with limited cutaneous systemic sclerosis 73.33% had Raynaud's phenomenon. 62.5% of the whole study population had Raynaud's phenomenon.

DISEASE SUBTYPES: % OF PATIENTS



PRSENCE OF RAYNAUD'S PHENOMENON

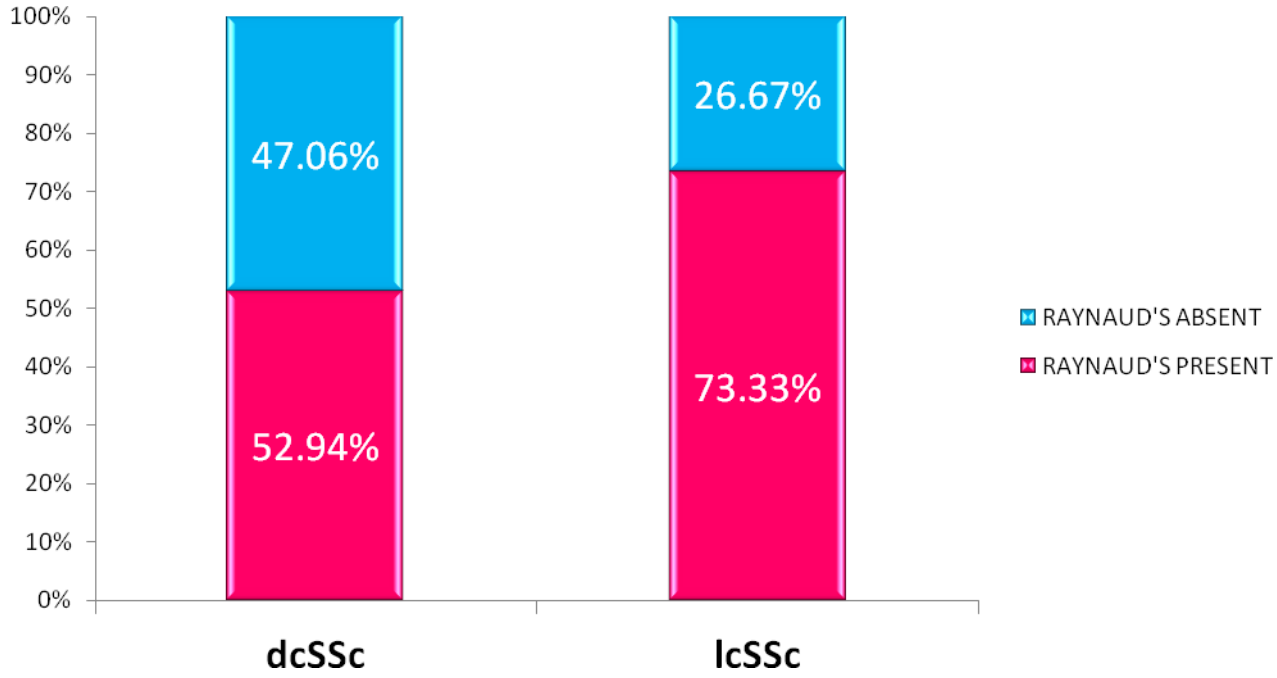


TABLE 6: PATTERN OF SYMPTOMS AMONG PATIENTS:

SYMPTOM	dcSSc - TOTAL 17		lcSSc - TOTAL 15	
	NO. OF PTS	%	NO.OF PTS	%
RAYNAUD'S PHENOMENON	9	52.95%	11	73.33%
ARTHRITIS	10	58.82%	12	80%
SICCA	4	23.53%	6	40%
DIFF.IN MOUTH OPENING	15	88.24%	14	93.33%
GERD	13	76.47%	14	93.33%
DYSPHAGIA	8	47.06%	12	80%

Both in dcSSc and lcSSc subsets of systemic sclerosis gastrointestinal symptoms predominate. 88.24% of patients with dcSSc had difficulty in opening of mouth and 76.47% of them had gastro oesophageal reflux symptoms. Among lcSSc subset patients the prevalence of these symptoms was 93.33%.

TABLE 7:

CARDIOPULMONARY SYMPTOMS AMONG PATIENTS

	dcSSc - TOTAL 17		lcSSc - TOTAL 15	
	NO. OF PTS	%	NO.OF PTS	%
DYSPNOEA	14	82.35%	13	86.67%
DRY COUGH	7	41.18%	9	60%
HAEMOPTYSIS	1	5.9%	0	0%
CHEST PAIN	3	17.65%	6	40%
PALPITATION	4	23.53	6	40%
SYNCOPE	0	0	2	13.33%

Among cardiopulmonary symptoms, in both subset of the disease dyspnoea on excertion is the predominating symptom. 82.35% of patients with dcSSc had dyspnoea and 86.67% of patients with lcSSc had dyspnoea on excertion. 41.18% of dcSSc patients and 60% of lcSSc patients had dry cough.

PATTERN OF SYMPTOMS AMONG PATIENTS

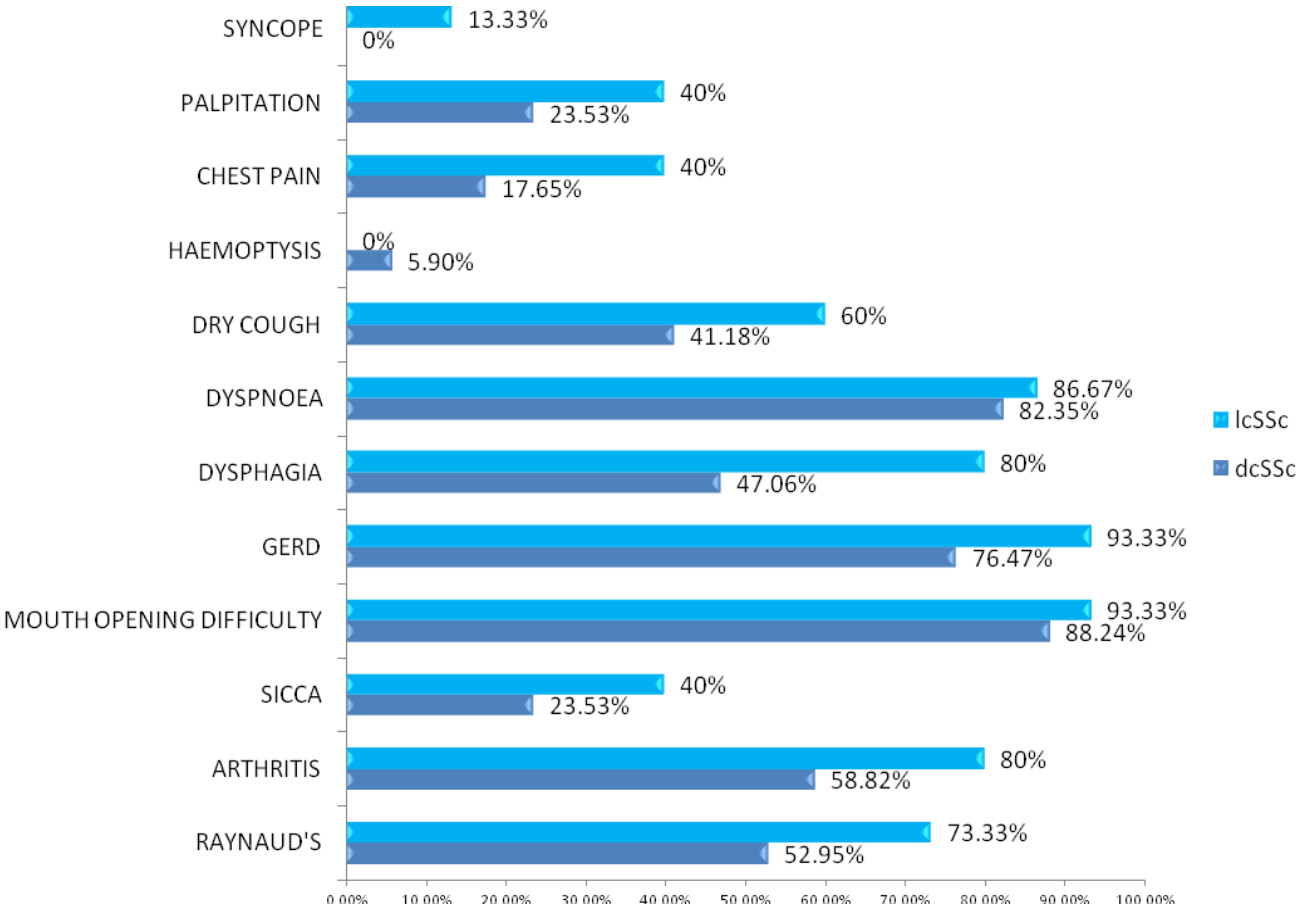


TABLE 8

CLINICAL PARAMETERS

	dcSSc – TOTAL 17		lcSSc – TOTAL 15	
CLINICAL FEATURES	NO.OF PTS	%	NO.OF PTS	%
CYANOSIS	0	0%	0	0%
CLUBBING	1	5.88%	5	33.33%
PEDAL EDEMA	4	23.53%	3	20%
HYPER PIGMENT	17	100%	13	86.67%
TELENGECTASIA	0	0%	0	0%
SALT&PEPPER	16	94.12%	11	73.33%
SKIN ULCER	4	23.53%	2	13.33%
CALCINOSIS CUTIS	0	0%	2	13.33%
STELLATE SCAR	17	100%	15	100%
MICROSTOMIA	16	94.12%	14	93.33%
FLEX.CONTRACTURE	10	58.82%	12	80%
SCLERODACTYLY	17	100%	15	100%
VELCRO CRACKLES	9	52.94%	7	46.67%
PLEURAL EFFUSION	0	0%	1	6.67%
↑ JVP	2	11.76%	1	6.67%
LPH	1	5.88%	1	6.67%
LOUD P2	4	23.53%	3	20%

Most of the patients had typical dermatological manifestations. All of them had pitted scar at the pulp of fingers in both the disease subtypes. All of them had sclerodactily also. 52.94% of patients with dcSSc and 46.67% of patients with lcSSc had Velcro crackles at their lung bases.

TABLE 9: DISEASE PARAMETERS

	dcSSc – TOTAL 17			lcSSc – TOTAL 15		
PARAMETER	RANGE	MEAN	SD	RANGE	MEAN	SD
DURATION	1-7	2.82	1.94	1-8	3.53	2.36
Hb g%	8.2-13.6	10.3	1.62	8.2-14.2	10.11	1.49
ESR mm/1st hr	52-133	40.58	20.38	5-100	35.07	24.57
MRSS	12-32	21.06	5.93	11-18	14.27	2.37

The average duration of the disease (dcSSc) is 2.82years and that of lcSSc is 3.53 years. The mean haemoglobin concentration is 10.3g% and 10.11g% respectively. dcSSc subset of patients had an average ESR of 40.58mm/1sthr and lcSSc patients had 35.07mm/1st hr. The Modified Rodnan Skin Score of patients with dcSSc ranges from 12 to 32 and the average score is 21.06. For patients with lcSSc the score ranges from 11 to 18 and the average score is 14.27.

TABLE 10: POSITIVE ANTIBODY PATTERN

ANTIBODY	dcSSc–TOTAL 17		lcSSc–TOTAL 15		TOTAL-32	
	Number	%	Number	%	Number	%
ANA	14	82.35%	13	86.67%	27	84.38%
Scl 70 antibody	6	35.29%	2	13.33%	8	25%
Anticentromere	0	0%	6	40%	6	18.75%

Anti nuclear antibody is positive in 82.35% of patients with dcSSc subset of the disease and in LlSSc subset the ANA positivity is 86.67%. The Scl 70 antibody is positive in 35.29% of patients with dcSSc and 13.33% of patients with lcSSc exhibits positivity to this antibody. Anti Centromere antibody is positive in 40% patients with lcSSc and none of the patients with dcSSc have anti centromere antibody.

POSITIVE ANTIBODY PATTERN

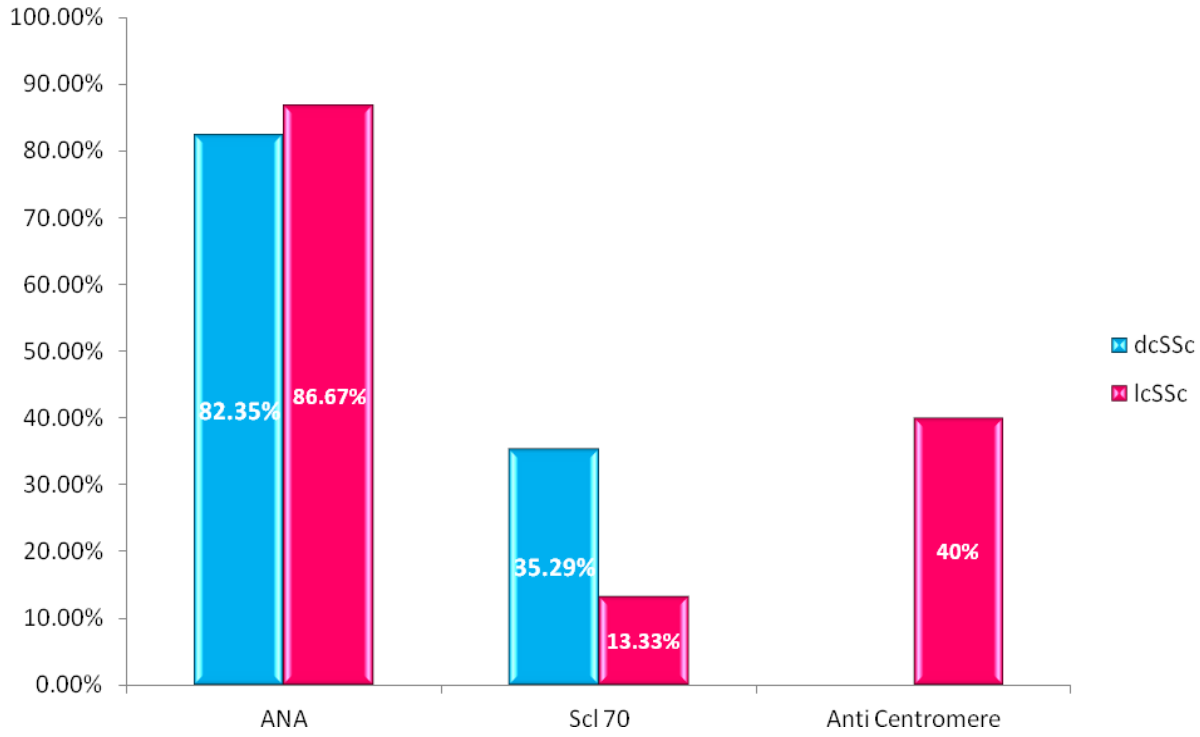


TABLE 11: ABNORMAL IMAGING REPORTS

	dcSSc –TOTAL 17		lcSSc–TOTAL15		TOTAL-32	
Investigation	Number	%	Number	%	Number	%
X-RAY CHEST	9	52.94%	11	73.33%	20	62.5%
HRCT CHEST	12	70.59%	12	80%	24	75%
PFT	11	64.71%	13	86.67%	24	75%

Among patients with dcSSc 52.94% has abnormal chest x-ray, 70.59% shows abnormal HRCT findings and 64.71% has abnormal PFT reports. In patients with lcSSc the abnormal reports are higher; 73.33% shows abnormal chest x-ray, 80%has abnormal HRCT findings and 86.6% has abnormal PFT reports.

ABNORMAL IMAGING REPORTS

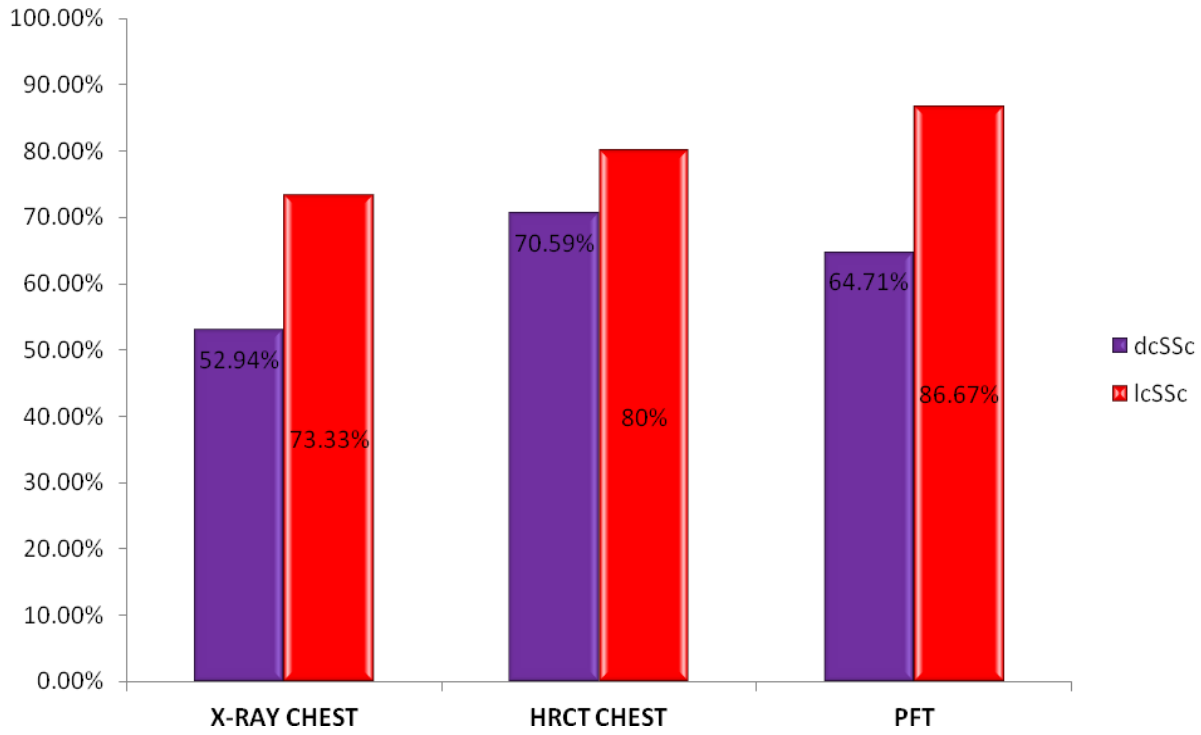


TABLE 12: CHEST X-RAY FINDINGS

	dcSSc –TOTAL 17		lcSSc –TOTAL 15		TOTAL-32	
FINDING	NO.	%	NO.	%	NO.	%
NORMAL	8	47.06%	4	26.67%	12	37.5%
RETICULAR	8	47.06%	11	73.33%	19	59.38%
VOL.LOSS	7	41.18%	5	33.33%	12	37.5%
PLEURAL EFFUSION	0	0%	1	6.67%	1	3.1%

Most common chest x-ray finding in dcSSc and lcSSc subset patients is reticular shadows (47.06% and 73.33% respectively). 1 patient with lcSSc had pleural effusion.

CHEST X-RAY FINDINGS

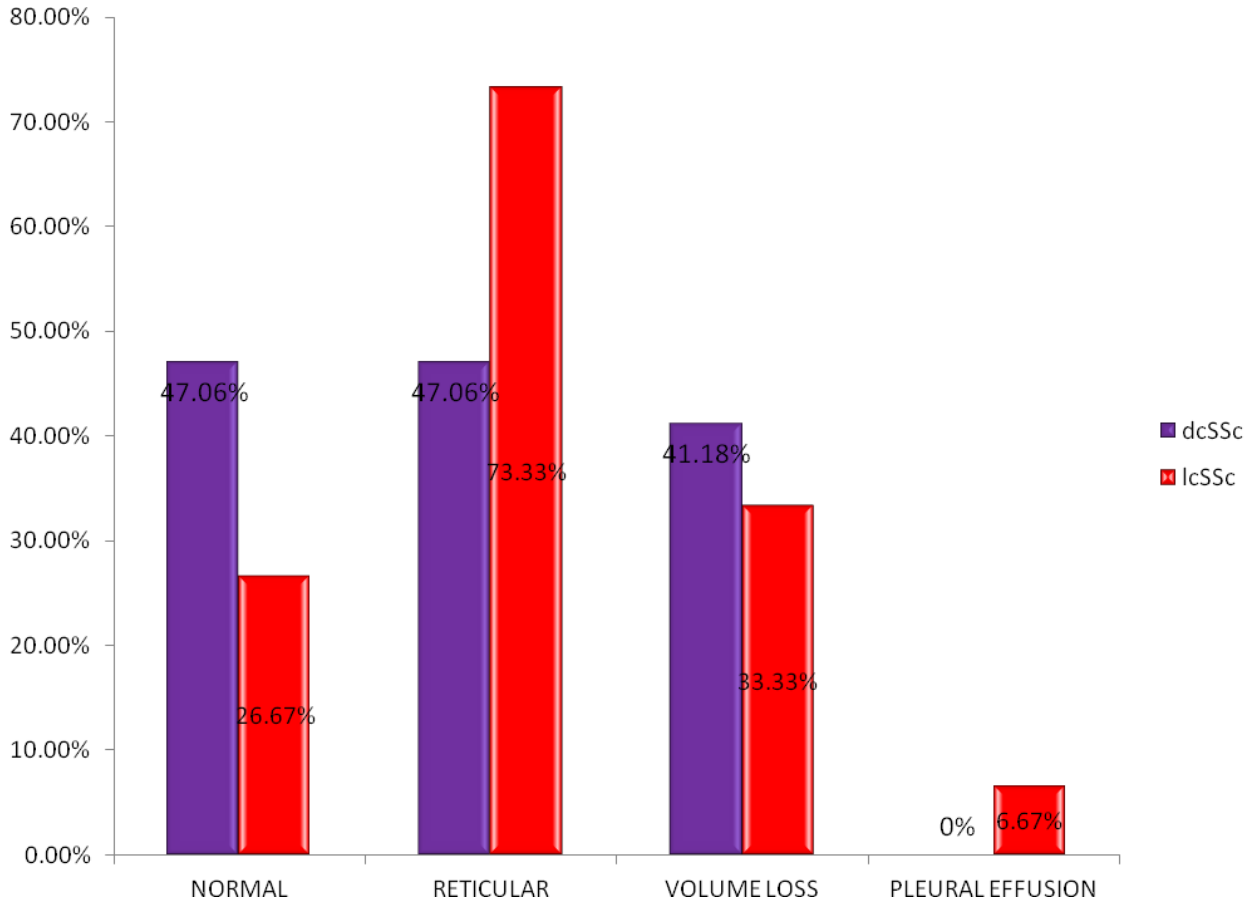


TABLE 13: HRCT FINDINGS

FINDINGS	dcSSc – TOTAL 17		lcSSc – TOTAL 15		Total – 32	
	No.	%	No.	%	No.	%
NORMAL	6	35.29%	3	20%	9	28.13%
GROUND GLASS OPACITY	10	58.82%	12	80%	22	68.75%
RETICULO NODULAR	5	29.41%	8	53.33%	13	40.63%
HONEY COMBING	10	58.82%	8	53.33%	18	56.25%
INTERLOBAR SEPTAL THICKENING	9	52.94%	10	66.67%	19	59.38%
PLEURAL THICKENING	8	47.06%	7	46.67%	15	46.88%
BRONCHIECTASIS	9	52.94%	7	46.67%	16	50%
NODULES	6	35.29%	6	40%	12	37.5%
MEDIASTINAL LN	2	11.76%	1	6.67%	3	9.38%
PLEURAL EFFUSION	1	5.88%	1	6.67%	2	6.25%

The common HRCT findings in patients with dcSSc are ground glass opacity (58.82%), honey combing (58.82%), inter lobar septal thickening (52.94%) and bronchiectasis (52.94%). In patients with lcSSc 80% patients shows ground glass opacity, 66.67% shows interlobar septal thickening and 53.33% shows reticulonodular and honey combing pattern. In both subset of disease 1 patient each has radiologically evident pleural effusion.

HRCT FINDINGS

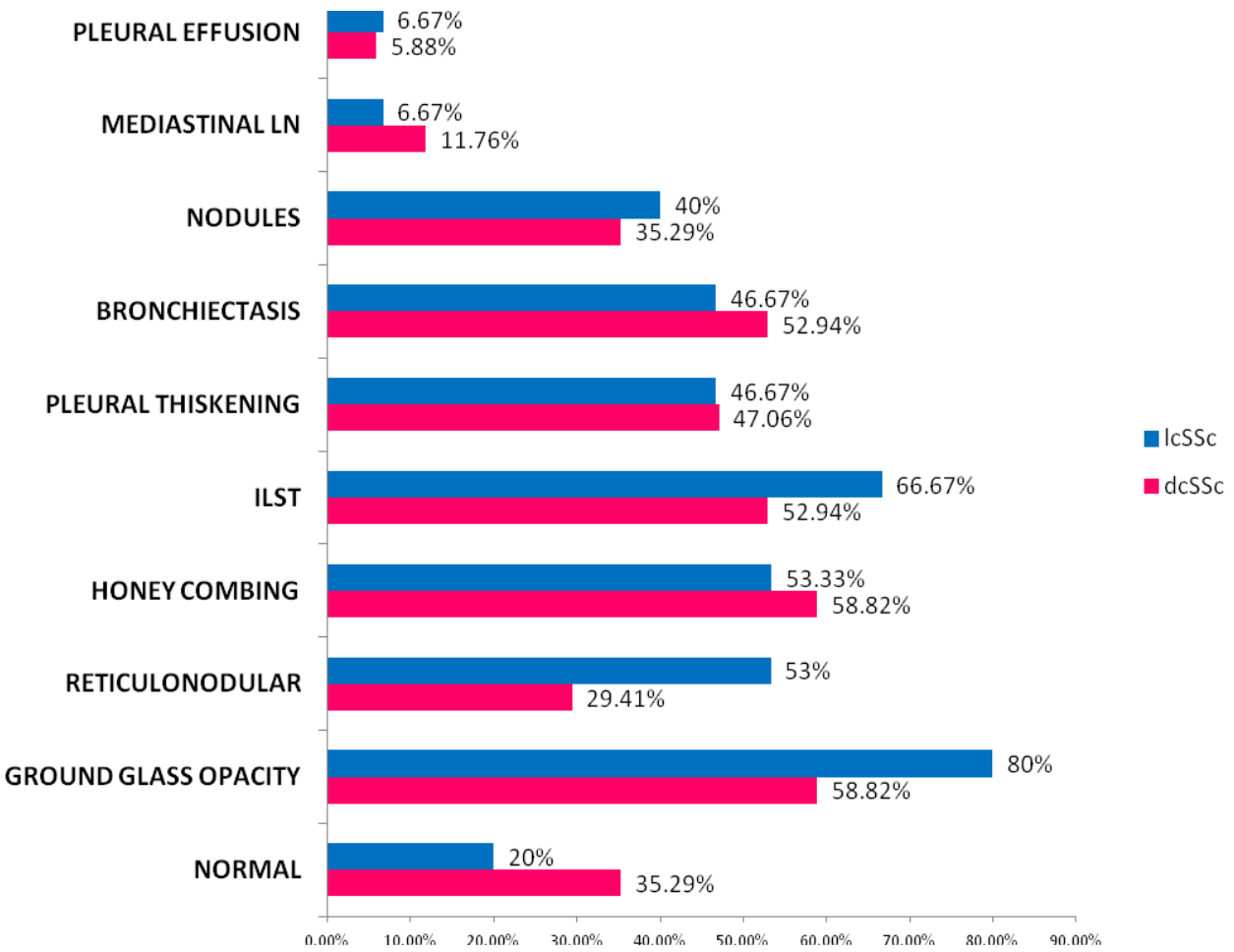


TABLE 14: PATTERN OF PFT FINDINGS

	dcSSc –TOTAL 17		lcSSc –TOTAL 15		TOTAL -32	
	NO.	%	NO.	%	NO.	%
NORMAL	6	35.29%	2	13.33%	8	25%
RESTRICTIVE	9	52.94%	13	86.67%	22	68.25%
OBSTRUCTIVE	2	11.76%	0	0%	2	6.25%

52.29% of patients with dcSSc show restrictive pattern in PFT and 11.76% shows obstructive pattern. Among patients with lcSSc 86.67% shows restrictive pattern in PFT. No patients with lcSSc has obstructive pattern in PFT.

PATTERN OF PFT FINDINGS

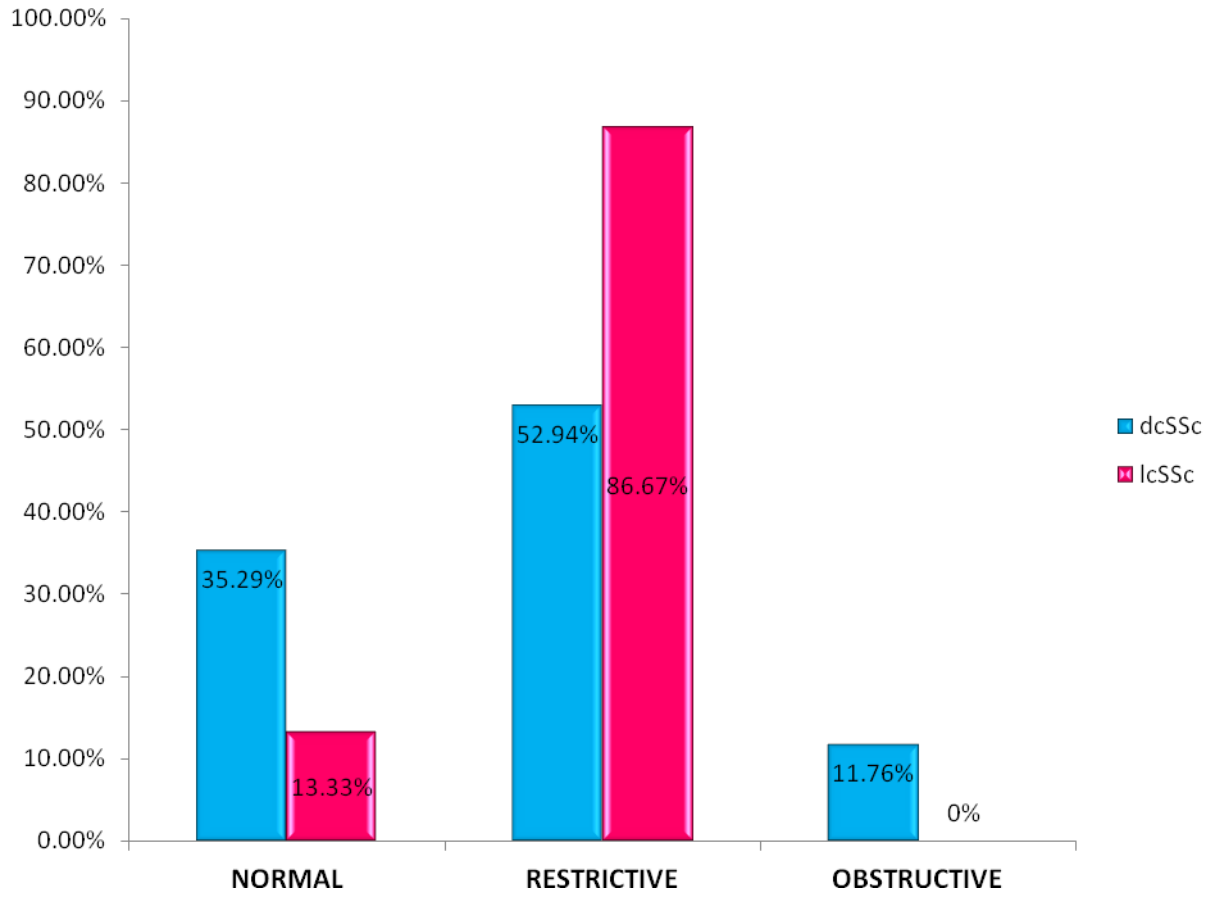


TABLE 15: PFT PARAMETERS

	dcSSc			lcSSc		
PARAMETER	RANGE	MEAN	SD	RANGE	MEAN	SD
FVC (Ltr)	1.02-4.41	1.81	0.83	0.87-2.74	1.60	0.48
FEV1 (Ltr)	0.38-4.17	1.46	0.83	0.85-2.34	1.48	0.41
FVC%	40-103	68.29	20.25	35-92	64	14.72
FEV1%	12-114	66.06	27.42	37-89	71	15.15
FEV1/FCV	14.7-100	81.37	20.41	85-100	92.99	3.76

The mean FVC% of dcSSc patients is 68.29% and the FEV1% is 66.06%. The average FEV1/FVC of patients with dcSSc is 81.37.

In patients with lcSSc, the mean FVC% is 64% and the mean FEV1% is 71%. They show an average FEV1/FVC of 92.99.

TABLE 16: SEVERTY OF RESTRICTIVE PATTERN:

SEVERTY	dcSSc		lcSSc		Total	
	NO.	%	NO.	%	No.	%
MILD	1	11.11%	5	38.46%	6	27.27%
MODERATE	5	55.56%	5	38.46%	10	45.45%
SEVERE	3	33.33%	3	23.08%	6	27.27%
TOTAL	9	100%	13	100%	22	100%

In patients with dcSSc and restrictive pattern in PFT 11.11% have mild restriction, 55.56% have moderate restriction and 33.33% have severe restriction in PFT.

Among patients with lcSSc and restrictive pattern in PFT 38.46% have mild restriction, 38.46% patients have moderate restriction and the remaining 23.08% have severe restriction.

Severity of restrictive pattern in pulmonary function test is classified according to percentage of predicted FVC(33,34).

Mild- 70-79%. Moderate- 50- 69% Severe - <50%

SEVERTY OF RESTRICTIVE PATTERN

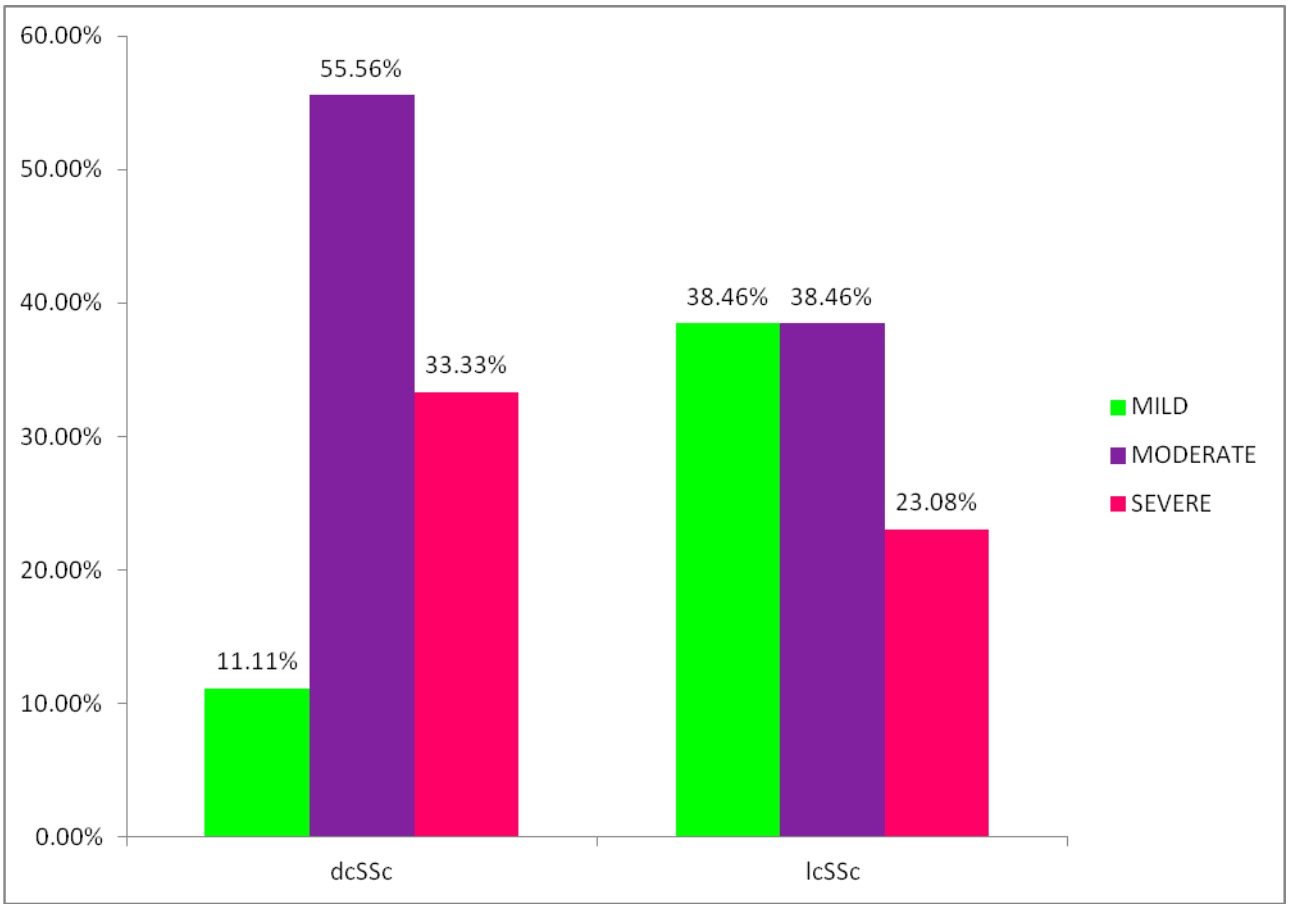


TABLE 17: PULMONARY MANIFESTATIONS

DISEASE	dcSSc – TOTAL 17		lcSSc – TOTAL 15		TOTAL 32	
	NO.	%	NO.	%	NO.	%
ILD	11	64.71%	13	86.67%	24	75%
OBSTRUCTIVE	1	5.88%	0	0%	1	3.13%
RESTRICT+OBS	1	5.88%	0	0%	1	3.13%
PLEURAL EFFUSIONEFFUSION	1	5.88%	1	6.67%	2	6.25%
PULMONARY HAEMORRHAGE	1	5.88%	0	0%	1	3.13%

The commonest pulmonary manifestation found in both subset of systemic sclerosis is interstitial lung disease. It is found in 64.71% of patients with dcSSc and in 86.67% patients with lcSSc. 1 patient with dcSSc had obstructive lung disease and another patient with dcSSc had pulmonary haemorrhage. 1 patient from both subset of disease had pleural effusion.

PULMONARY MANIFESTATIONS

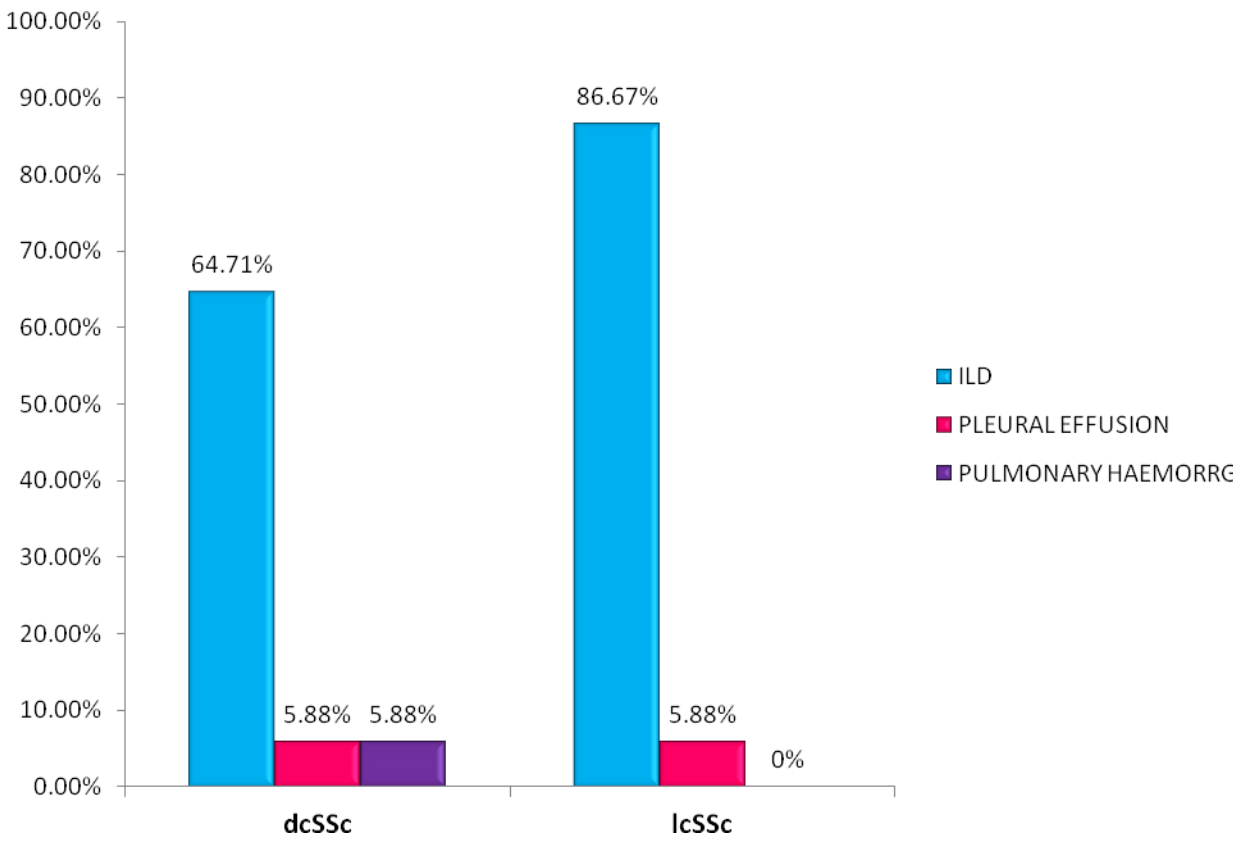


TABLE 18 : ILD IN dcSSc

SL NO.	PARAMETER	ILD PRESENT	ILD ABSENT	TOTAL	'P' VALUE
Sex	Male	2	4	6	0.0452
	Female	9	2	11	
Duration of symptoms	≤4 years	7	6	13	0.0908
	>4 years	4	0	4	
MRSS	≤17	1	4	5	0.0126
	>17	10	2	12	
Scl 70	Positive	5	1	6	0.2146
	Negative	6	5	11	
Anti Centromere Antibody	Positive	2	0	2	0.2635
	Negative	9	6	15	
PFT	Normal	1	5	6	0.0021
	Abnormal	10	1	11	

33.33% of male patients with dcSSc had ILD while 81.82% of female patients with dcSSc had ILD. There is a statistically significant relationship between sex and ILD in patients with dcSSc (‘P’ value is 0.0452).

Among those patients with dcSSc and duration of symptoms ≤4 years 53.85% had ILD. All patients with duration of symptoms >4 years and dcSSc had ILD. The ‘P’ value for this relation is 0.0908 which implies there is no significant relation exists between these two parameters.

Only 20% of patients with dcSSc and Modified Rodnan Skin Score ≤17 had ILD. But 83.33% of patients with MRSS >17 had ILD. The ‘P’ value for this relationship is 0.0126 and there is significant relation exists between these two parameters.

83.33% of the patients with positive Scl 70 antibody had ICD in the dcSSc subset. But 54.54% of dcSSc patients with negative Scl 70 antibody had ILD. The ‘P’ value for this association is 0.2146; ie there no statistically significant relationship exists between these two parameters. Similarly there is no significant relationship exists between anticentromere antibody and ILD in patients with dcSSc.

There is a significant association between abnormal PFT and ILD. 10 out of 11(90.9%) patients with abnormal PFT had ILD. Only 1 patient out of 6 with normal PFT has ILD (16.67%).

TABLE 19: ILD IN lcSSc

SL NO.	PARAMETER	ILD PRESENT	ILD ABSENT	TOTAL	'P' VALUE
Sex	Male	0	0	0	Cannot be calculated
	Female	13	2	15	
Duration of Disease	≤4 years	8	2	10	0.2825
	>4 years	5	0	5	
MRSS	≤12	4	1	5	0.5934
	>12	9	1	10	
Scl 70	Positive	2	0	2	Cannot be calculated
	Negative	11	2	13	
Anti Centromere Antibody	Positive	5	1	6	0.756
	Negative	8	1	9	
PFT	Normal	0	2	2	0.0001
	Abnormal	13	0	13	

In the study population, all the patients with lcSSc are females. Among them 13 out of 15 (86.67%) had ILD. There are no male patients with lcSSc in the study population.

80% of lcSSc patients with disease duration ≤4 years had ILD and all the lcSSc patients with disease duration >4 years had ILD. There is no

statistically significant association between duration of lcSSc and development of ILD.

80% of lcSSc patients with MRSS ≤12 and 90% of lcSSc patients with MRSS >12 had ILD. There is no statistically significant association between MRSS and development of ILD.

13.33% of lcSSc patients had Scl 70 antibody positivity and all of them had ILD. But 84.62% of Scl 70 negative lcSSc patients also had ILD. There is no statistically significant association between the Scl 70 antibody and development of ILD in lcSSc patients.

40% of lcSSc patients had positive anti centromere antibody and among them 83.33% had ILD. 88.89% of anti centromere antibody negative lcSSc patients also had ILD. Here also no statistically significant association exists between anti centromere antibody and development of ILD in lcSSc patients.

All the 13 lcSSc patients with abnormal PFT had ILD and both the 2 lcSSc patients with normal PFT do not have ILD. The ‘P’ value for this association is 0.0001.

TABLE 20: ILD IN SYSTEMIC SCLEROSIS SUBTYPES

	ILD PRESENT		ILD ABSENT		TOTAL		'P' VALUE
	Number	%	Number	%	Number	%	
dcSSc	11	64.70%	6	35.30%	17	100%	0.1524
lcSSc	13	86.67%	2	13.33%	15	100%	

64.70% of dcSSc patients and 86.67% of lcSSc patients had ILD and the 'P' value for this association is 0.1524 which means there is no statistically significant association between the subtypes of the disease and the development of ILD.

ILD IN SYSTEMIC SCLEROSIS SUBTYPES

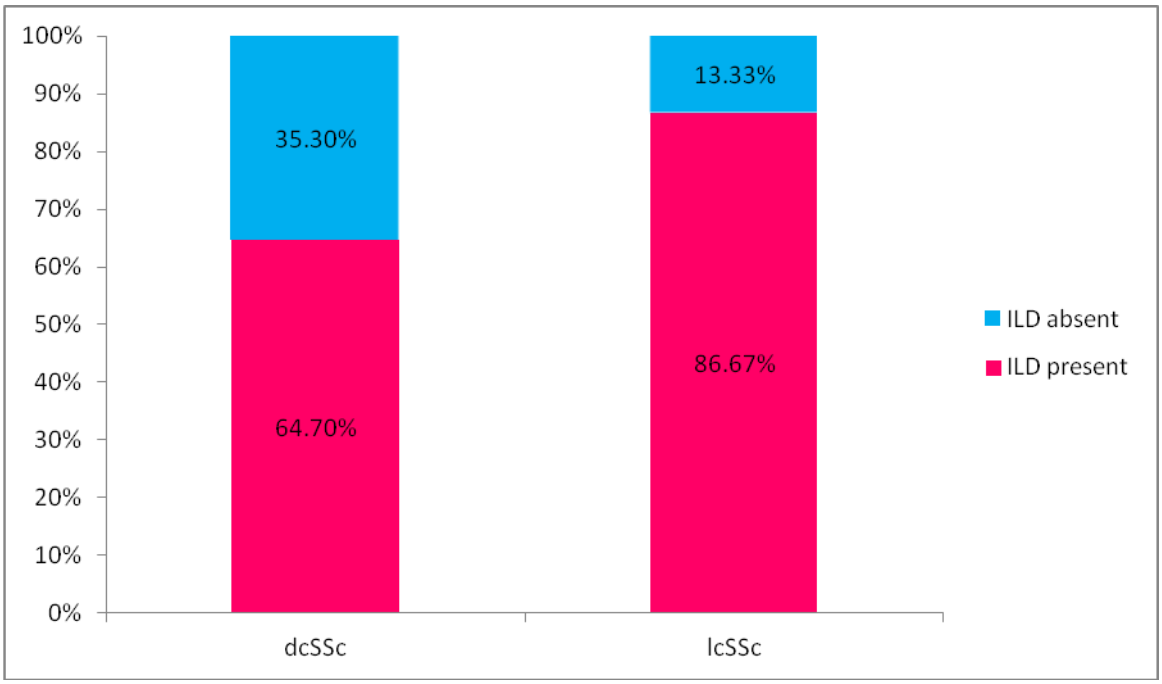


TABLE 21: CARDIOVASCULAR PARAMETERS

PARAMETER	dcSSc			lcSSc		
	RANGE	MEAN	SD	RANGE	MEAN	SD
PULSE	68 - 108	87	9.5	70 – 120	89	15
SYSTOLIC BP	90 - 220	116	29	200 – 90	117	25
DIASTOLIC BP	60 - 140	75	18	70 – 90	74	7.4
LVEF%	45 - 63	56.6	5.78	48 – 70	57.9	6.62

In dcSSc subset of patients only one patient had systemic hypertension and she was admitted in the hospital with renal crisis. One patient in the lcSSc subset also had systemic hypertension and she had concomitant chronic kidney disease.

TABLE 22: ECG CHANGES

PARAMETER		dcSSc-TOTAL 17		lcSSc-TOTAL15		TOTAL	
		NO.	%	NO.	%	NO.	%
Axis	Normal	12	70.59%	11	73.33%	23	71.86%
	RAD	4	23.53%	2	13.33%	6	18.75%
	LAD	1	5.88%	2	13.33%	3	9.38%
Arrhythmia		0	0%	0	0%	0	0%
CAD		0	0%	0	0%	0	0%
Conduction Block	RBBB	1	5.88%	0	0%	1	3.13%
	LBBB	0	0%	0	0%	0	0%
	LAHB	1	5.88%	1	6.67%	2	6.25%
	LPHB	1	5.88%	1	6.67%	2	6.25%
	RBBB+LAHB	0	0%	1	6.67%	1	3.13%
	None	14	82.35%	12	80%	26	81.25%

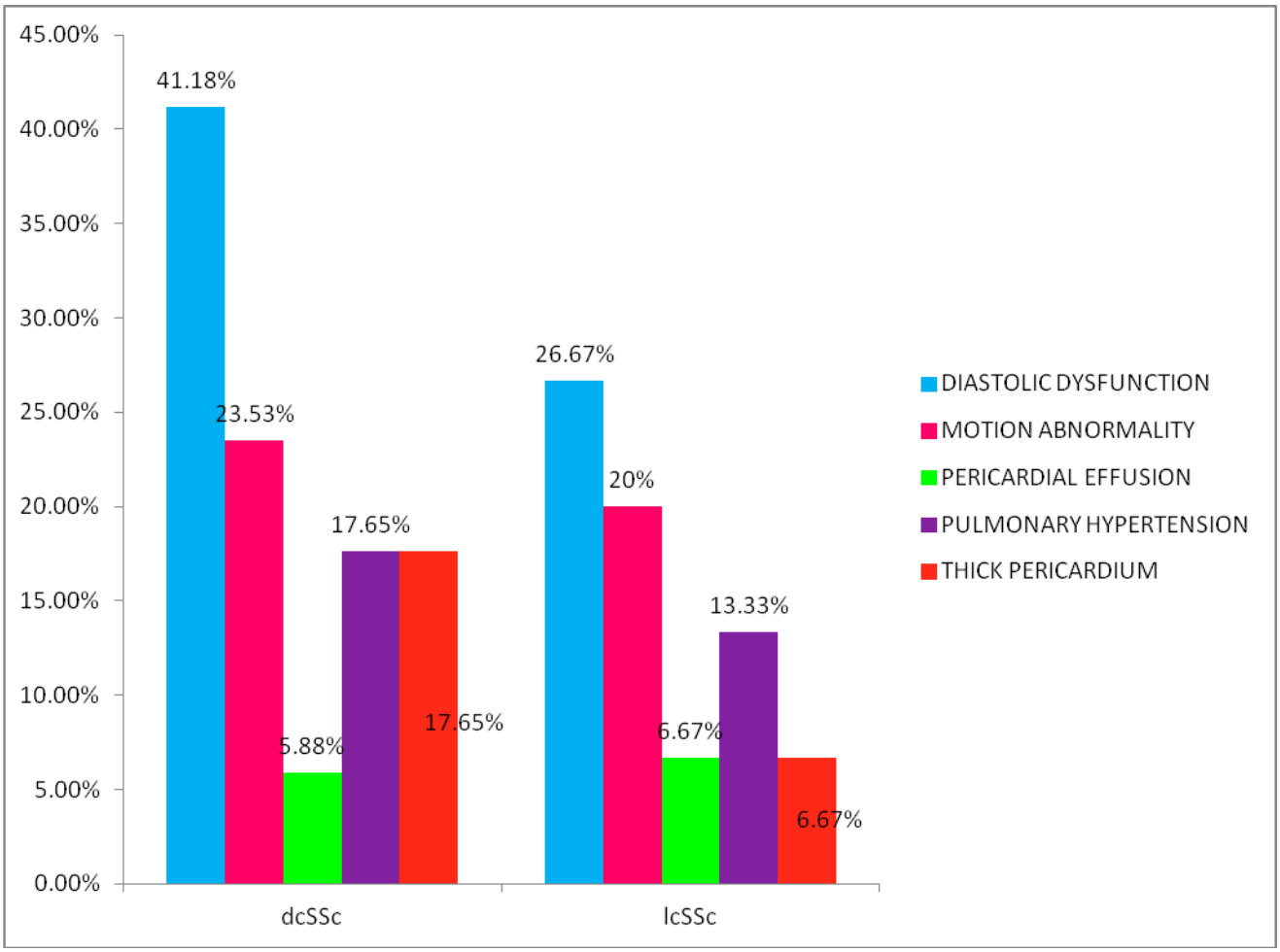
In the study population 23 patients (71.86%) had normal axis on ECG. 6 patients (18.75%) had right axis deviation of which 4 are dcSSc patients and 2 are lcSSc patients. 3 patients (9.38%) had left axis deviation. None of the patients showed arrhythmia or abnormal Q waves in ECG from both the subset of disease. 1 patient from the dcSSc subset had RBBB. None had LBBB. 2 patients (6.25%), one from each subset had LAHB. Another 2 patients (6.25%), one from each subset had LPHB. 1 patient from the lcSSc subset had RBBB+LAHB.

TABLE 23: ECHO FINDINGS

PARAMETER	dcSSc – Total 17		lcSSc – Total 15		TOTAL – 32	
	Number	%	Number	%	Number	%
Diastolic Dysfunction	7	41.18%	4	26.67%	11	34.38%
Motion abnormalities	4	23.53%	3	20%	7	21.86%
Pericardial effusion	1	5.88%	1	6.67%	2	6.25%
Pulmonary Hypertension	3	17.65%	2	13.33%	5	15.63%
Thick Pericardium	3	17.65%	1	6.67%	4	12.5%

11 out of 32 (34.38%) patients had diastolic dysfunction, 7 in the dcSSc and 4 in the lcSSc subsets. 7 patients (21.86%) showed motion abnormalities in the form of paradoxical septal motion and hypokinesia. 2 patients (6.25%) had pericardial effusion, one patient from each subset. 5 patients(15.63%) had pulmonary artery hypertension of which 3 patients had dcSSc and 2 patients had lcSSc. 4 patients in the study group (12.5%) had thick pericardium.

ECHO FINDINGS



DISCUSSION

Systemic sclerosis (SSc) is a connective tissue disorder of unknown etiology, with heterogeneous clinical manifestations, and chronic and often progressive course, which affects the connective tissue of the skin, internal organs and the walls of blood vessels. Virtually it affects all the organ system of the body. A variety of pulmonary and cardiovascular manifestations are associated with systemic sclerosis and these are the major cause of morbidity and mortality in these patients.

In our study we selected 32 patients with systemic sclerosis from various IP & OP departments of Govt. Rajaji Hospital. Madurai. These patients were fulfilled the American College of Rheumatology criteria for the diagnosis of systemic sclerosis.

In this study the disease predominantly affects females. The female to male ratio in this study population is 4.33:1. According to Davidson's principles and practice of medicine there is a 4:1 female preponderance (23). In a study conducted by Haustein et al the overall female/male ratio was reported as 3:1.(3,24)

In this study the average age of patients is 39.28 years. 58.38% of the study population comes under the age group of 30-49 years. According to Harrison's principle of internal medicine (2) the most

common age of onset of this disease is in the range of 30-50 years. In Poormoghim et al study the average age was 40.9 years(25).

The mean duration of the disease is 3.16±2.11 years in our study population. 65.62% patients had the symptoms for a period of 1-3 years. According to Vinod K Sharma et al (26) the mean duration of the disease is 6.49 ± 4.34 years.

In this study 53.12% of the study population had diffuse cutaneous systemic sclerosis and the rest 46.88% had limited cutaneous systemic sclerosis. According to LeRoy et al more than 50 % of SSc patients belong to the limited SSc(11).

In the study 52.94% of dcSSc patients and 73.33% of lcSSc patients had history of Raynaud's phenomenon and a total of 62.5% of the study population had the same. But most of the literature describes a prevalence of >90% of Raynaud's phenomenon in patients with SSc. According to Haustein et al(3) Raynaud's phenomenon is seen in 98 % of SSc patients and it is a forerunner of SSc. In the AIIMS study by Vinod K Sharma et al (26) the prevalence of Raynaud's phenomenon was 92.2%. Most of my patients in the study population were dark coloured. It may be the reason why a low proportion of the study population had this phenomenon comparing to the literature.

The most common symptom of the patients in the study group was difficulty in opening mouth (90.63%). The most common cardiorespiratory symptom in the study population was dyspnoea (84.38%) followed by dry cough (50%). According to Baron et al(27) up to 50% of patients with systemic sclerosis (SSc) have complaints of dyspnoea. In an Indian study done in AIIMS, 55.5% patients had restriction of mouth opening and 51.1% patients had dyspnea(26).

All patients in the study population had pitted scar at the finger tip and sclerodactily. 84.38% had salt and pepper lesions and 93.76% patients had microstomia. The most common respiratory finging was Velcro crackles(50%).

The mean duration of the disease in the study group was 3.16±2.11 years. According to Terry et al(27) the mean duration is 2.48±1.68 years. The mean haemoglobin of the patients was 10.2±1.5g/dl and the mean ESR was 38±22.2mm/1st hr. The Modified Rodnan Skin Score of patients in the study population was 17.8±5.7. According to Terry et al(27) the mean Modified Rodnan Skin Score was 15.1 ± 12.0. According to Vinod K Sharma et al (26) the mean Rodnan score was 25.81 +/- 10.04.

84.38% of the study population showed ANA positivity. According to Terry et al the ANA positivity is 94% (27). According io Cleveland

clinic antinuclear antibody (ANA) is positive in 60% to 80% of patients with scleroderma (28). In the AIIMS study by Vinod K Sharma et al (26) ANA was positive in 89.1% patients(26). Scl 70 antibody was positive in 35.29% of dcSSc patients in the study population and anti centromere antibody was positive in 40% of lcSSc patients in the study group. According to Haustein et al (3) Scl 70 antibody is present in 21 – 40% of patients with dcSSc and anti entromere antibody is present in 40 – 57% patients with lcSSc.

In the study population 62.5% of patients had abnormal chest x-ray findings, 75% of patients had abnormal HRCT finding and 75% patients had abnormal PFT findings. In a study conducted by Totanarungroj et, they detected abnormal chest x-ray in 90% patients with SSc and abnormal HRCT in 100% patients with SSc. According to Seely et al (30) 73% patients had abnormal HRCT finding.

The most common HRCT finding in the study population were ground glass opacity (68.75%),interlobar septal thickening(59.38%) and honey combing(56.25%). According to Totanarungroj et al (29), the most common finding was interlobar septal thickening (85%%) followed by traction bronchiectasis (75%) and honey combing(40%). In their study the ground glass opacity was found in 25% patients.

75% of the study population had abnormal pulmonary function test. In a study conducted at AIIMS (26) the prevalence of abnormal PFT in systemic sclerosis patient was 85.8% and according to Krishnamoorthy et al who conducted similar study in south India it is 55% (31).

In our study among the patients with restrictive PFT 27.27% had mild restriction, 45.45% had moderate restriction and the rest 27,27% had severe restriction. According to Virginia D et al (32) 27% had moderate restriction and 13% had severe restriction.

The prevalence of ILD in our study population was 75%. According to Winklehner (35) et al it is 55%. According to Richard et al (36) ~90% % of SSc patients have been found to have pulmonary interstitial fibrotic changes at postmortem examination or on high-resolution computed tomography (HRCT) of the chest, only ~40% develop moderate or severe restrictive pulmonary disease on physiologic pulmonary function testing (forced vital capacity [FVC] of ≤75% of predicted). According to Harrison's principles of internal medicine clinically significant ILD develops in 16–43% of patients with SSc and some evidence of ILD can be found in up to 90% of patients with SSc at autopsy and 85% by thin-section high-resolution computed tomography (HRCT).

In our study there is no significant association between ILD and subtype of systemic sclerosis. 64.70% of dcSSc patients and 86.67% of lcSSc patients had ILD in the study population.

In dcSSc patients who were affected by ILD there is a significant association with sex, MRSS and PFT findings. Female sex and patients with MRSS score >17 are having statistically significant more chance for the development of ILD. But there is no significant association with duration of disease or antibody profile to the development of ILD in this subset of patients. In lcSSc subset of patients there is no statistically significant association with development of ILD and duration of disease, MRSS >12, & antibody profile.

In the study population 28.14% patients had axis deviation in ECG. None of the patients had arrhythmias or ischemic changes in ECG. 18.75% of patients had some degree of conduction block, of which LAHB and LPHB predominates (6.25% each). According to Poormoghim et al (25) the prevalence of abnormal axis in ECG is 10.3%, arrhythmia 3.5%, ischemic changes 1.7% and conduction block 13.8%.

34.38% of the patients had diastolic dysfunction. 21.86% patients had some degree of motion abnormalities. 6.25% patients had pericardial effusion and 12.5% patients had thick parietal pericardim. According to

Tünde Pintér et al(38) the prevalence of diastolic dysfunction is 79.2% in patients with systemic sclerosis. In Poormoghim et al (25) study 15.4% of patients had pericardial effusion. In the Janosik et al (37) study, pathological involvement of the pericardium was observed in 70%-80% of the patients at autopsy, while clinical manifestation was present in 7%-20% of the study subjects. They reported an association between pericardial effusion and cardiac involvement; pericardial effusions were small or large and had developed rapidly in some cases due to renal failure. In our study one patient with pericardial effusion had acute renal crisis. In Fischer et al (40) study 49% 0f patients with systemic sclerosis had a thick pericardium.

15.63% patients had pulmonary hypertension (17.65% of dcSSc patients and 13.33% of lcSSc patients). All of the patients with pulmonary hypertension had associated ILD also. None of the patients in the study population had isolated pulmonary hypertension. According to Robyn et al (39) the incidence of PAH related to SSc ranges from 4% to 35%, with slightly more PAH cases associated with lcSSc than with dcSSc. In some series, 50% to 90% of SSc patients with PAH had lcSSc, whereas 8% to 50% had dcSSc. Others have reported 13% to 50% of lcSSc patients develop PAH. The prevalence of PAH related to SSc correlates with the underlying systemic disease, ie, more often in women

35 to 55 years of age. According to Harrison's principles of internal medicine approximately 15% of SSc patients have PAH that can occur in association with ILD or as an isolated pulmonary abnormality. According to Diotet al incidence of PAH is 15–35% in patients with limited cutaneous SSc, usually as isolated PAH, and 30% in patients with diffuse cutaneous SSc, frequently associated with pulmonary fibrosis (41).

CONCLUSIONS

1. Sex ratio of male to female in this study is 1:4.33
2. Most patients are distributed under the age group 40 – 49 years
3. 65.62% patients had the symptoms for a period of 1-3 years only.
4. 53.12% had dcSSc and 46.88% had lcSSc subsets of disease.
5. Patients with Raynaud's phenomenon are 62.5%.
6. Restricted mouth opening is the most common symptom and dyspnoea on excertion is the most common cardiopulmonary symptom
7. All patients had digital stellate scar and sclerodactyly.
8. ANA is positive in 84.38% of patients. Scl 70 antibody is positive in 35.29% of patients with dcSSc and anticentromere antibody is positive in 40% of patients with lcSSc
9. 68.25% patients had restrictive lung disease in PFT.
10. The most common pulmonary manifestation is ILD in the study group. 75% of the studied population had ILD.
11. 34.38% patients had diastolic dysfunction, 6.25% patients had pericardial effusion and 15.63% patients had pulmonary hypertension.

LIMITATIONS

1. The study group contains 32 patients only.
2. Investigations like diffusion study, cardiac catheterization and broncho alveolar lavage could not be done.
3. No male patients were there with lcSSc.

SUMMARY

The study ‘Cardiopulmonary Manifestations of Systemic Sclerosis’ is a descriptive study conducted on patients with systemic sclerosis who were treated in Govt. Rajaji Hospital, Madurai. Thirty two patients were included in the study and were investigated to detect the presence of various cardiac and pulmonary manifestations of systemic sclerosis.

Analyzing the data shows a female preponderance of the disease in the study population with a female to male ratio of 4.33:1. Diffuse cutaneous subtype of the disease is more in number than the limited cutaneous subtype. Dyspnoea was the most common cardiopulmonary symptom. 62.5% of the patients had Raynaud’s phenomenon. ILD was the most common pulmonary manifestation with a prevalence of 75%. 6.25% patients had pleural effusion. 34.38% patients had diastolic dysfunction and 6.25% patients had pericardial effusion. 15.63% of them had pulmonary artery hypertension and all of them are associated with interstitial lung disease.

GLOSSARY

SSc	-	Systemic Sclerosis
dcSSc	-	Diffuse Cutaneous Systemic Sclerosis
lcSSc	-	Limited Cutaneous Systemic Sclerosis
ESR	-	Erythrocyte sedimentation rate
Hb	-	Hemoglobin
MRSS	-	Modified Rodnan Skin Score
PFT	-	Pulmonary function test
HRCT	-	High resolution computed tomography
FVC	-	Forced vital capacity
FEV1	-	Forced expiratory volume in first one second
FEF	-	Forced expiratory flow
ILD	-	Interstitial lung disease
IPF	-	Idiopathic pulmonary fibrosis
Scl-70	-	Anti topoisomerase 1 antibody

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PROFORMA

CARDIO PULMONARY MANIFESTATIONS OF SYSTEMIC SCLEROSIS

Name: Age: Sex:
IP No:

Address:
Phone No:

Clinical features:

Raynaud's phenomenon	Dyspnoea
Arthritis	Palpitation
Muscle weakness	Chest pain
Dry mouth	Syncope
Dry eyes	Dry cough
Difficulty in opening mouth	Haemoptysis
GER	Dysphagia

Past History

HTN/DM/TB/BA/ATT/CAD/COPD/RHD/Pneumothorax

Personal History

Smoking

Family History

HTN/DM/CAD/TB/BA

VITALS

PR:

BP: RR:

GENRAL EXAMINATION

Pallor: Cyanosis:

Clubbing: Pedal oedema:

DERMATOLOGICAL

Hyper pigmentation: Calcinosis cutis:

Telengectasia: Pitted scars on pulp of fingers:

Salt & Pepper lesions: Microstomia:

Skin ulcers: Skin thickening:

CVS System Musculoskeletal

JVP Carpel Tunnel Syndrome:

LVH Flexon contractures of fingers

Heart sounds Sclerodactily

Murmurs Tendon Friction Rubs

RS Others

Velcro Rales:

Added sounds:

Pleural effusion:

INVESTIGATIONS

Hb:	RBS:	ANA:
TC:	UREA:	Scl 70:
DC:	CREATININE:	
Anticentromere		

ESR:

Platelet Count:

Peripheral smear:

ECG:

ECHO:

CXR:

HRCT:

PFT:

serial no.	NAME	age	sex	D.duration	Raynaud's	Arthritis	Sicca	dif.mouth op	GERD	dysphagia	dyspnoea	dry cough haemoptysis	haemoptysis	palpitation	chest pain	syncope	PR	SBP	DBP	RR	cyanosis	dcSSc	lcSSC	MRSS
1	Akhila	32	F	7	Y	Y	N	Y	Y	Y	Y	Y	N	N	N	N	92	110	70	28	N	Y		28
2	Chellapandi	24	M	1	Y	Y	N	Y	Y	N	Y	Y	Y	N	N	N	84	100	70	22	N	Y		31
3	Meena	45	F	1	Y	N	N	Y	N	N	Y	N	N	N	N	N	108	100	60	20	N	Y		32
4	Mariyammal	40	F	1	Y	Y	N	Y	Y	Y	Y	N	N	N	N	N	70	90	70	24	N		Y	12
5	Sathish Kumar	20	M	1	N	N	N	Y	N	N	N	N	N	N	N	N	84	110	70	18	N	Y		14
6	Nagajyothi	40	F	7	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	90	110	70	22	N		Y	12
7	Alamelu	43	F	3	N	Y	N	Y	Y	N	Y	N	N	Y	N	N	92	110	70	26	N	Y		30
8	Seeniyamal	50	F	2	Y	Y	N	Y	Y	Y	Y	Y	N	Y	N	Y	76	200	90	20	N		Y	14
9	Kavitha	30	F	3	Y	Y	N	Y	Y	Y	Y	N	N	N	N	N	86	110	70	16	N		Y	16
10	Suganthini	31	F	7	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	120	100	70	32	N		Y	18
11	Gayathri	20	F	3	Y	Y	N	Y	N	N	Y	N	N	N	N	N	76	110	70	20	N	Y		12
12	Pothumani	35	F	5	Y	N	Y	Y	Y	Y	Y	Y	N	N	N	N	108	120	70	44	N		Y	12
13	Balamurugan	29	M	2	N	Y	N	N	Y	Y	Y	N	N	N	N	N	86	90	60	20	N	Y		21
14	Kanakavally	40	F	2	N	Y	Y	Y	Y	Y	N	Y	N	Y	N	N	90	104	70	16	N		Y	14
15	Malathy	51	F	1	N	N	N	Y	Y	Y	Y	Y	N	N	Y	N	110	110	70	40	N		Y	13
16	Vellaiyammal	47	F	1	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	90	220	140	30	N	Y		16
17	Rajangam	55	M	2	N	N	N	Y	Y	N	N	N	N	N	N	N	96	110	70	34	N	Y		17
18	Malar	35	F	5	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	78	120	80	22	N		Y	12
19	Lakshmi	55	F	1	N	N	N	N	Y	N	Y	N	N	N	Y	N	80	120	80	18	N	Y		18
20	Muniyammal	56	F	4	N	Y	N	Y	Y	N	Y	N	N	Y	Y	N	90	100	70	18	N		Y	16
21	Mehraj Beeegum	28	F	8	Y	Y	N	Y	N	Y	Y	N	N	N	Y	N	92	110	70	24	N		Y	17
22	Vasantha	40	F	2	Y	Y	N	Y	Y	N	Y	Y	N	N	Y	N	84	130	90	18	N		Y	18
23	Mariyammal	50	F	1	N	Y	Y	Y	Y	N	Y	N	N	N	N	N	96	90	60	22	N	Y		18
24	Anandi	35	F	1	N	Y	Y	Y	Y	Y	Y	N	N	Y	N	N	96	126	80	26	N		Y	13
25	Selvapandi	28	M	2	Y	Y	N	Y	Y	Y	Y	Y	N	N	N	N	84	130	80	20	N	Y		19
26	Rathinam	58	F	3	Y	Y	N	N	Y	N	N	N	N	N	N	N	76	110	70	18	N		Y	11
27	Janaki	36	F	5	Y	Y	N	Y	Y	Y	Y	Y	N	Y	N	N	92	120	70	26	N	Y		20
28	Fathimuthu	47	F	6	Y	N	N	Y	Y	Y	Y	Y	N	Y	N	N	68	110	70	20	N	Y		22
29	Vijayalakshmi	33	F	4	N	N	N	Y	Y	Y	Y	N	N	N	N	N	78	120	80	16	N	Y		21
30	Duraipandi	45	M	3	Y	N	Y	Y	N	N	N	Y	N	N	N	N	82	110	70	18	N	Y		17
31	Poongodi	30	F	2	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	70	116	70	24	N		Y	16
32	Parameswari	49	F	5	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	96	110	80	28	N	Y		22

pl.effusion	velcro rales	Flex.contract	clubbing	pedal oedema	salt&pepper	ulcer	microstomia	hyper pigmnt	telengect	c.cutis	stellate scar	sclerodactily	tend fr.rub	JVP	LPH	Loud P2	murmurs	Hb g%	ESR mm/1hr	RBS mg%	Creatinine mg%	ANA	Scl 70	anti centromere	CXR	reti.shad
N	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	N	10.8	65	98	1.1	N	P	N		Y
N	N	N	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	Y	N	11	32	67	0.8	P	N	N		N
N	Y	N	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	11	46	103	1.2	N	P	N		Y
N	N	Y	Y	Y	N	N	Y	Y	N	N	Y	Y	N	N	N	N	N	10	55	118	1.6	P	N	P		Y
N	N	N	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	12.2	25	70	0.7	N	P	N		N
N	N	N	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	11	12	75	0.8	P	N	N		Y
N	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	N	N	N	N	9.7	88	98	0.8	P	N	N		Y
N	N	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	8.2	42	64	2.1	P	N	P		Y
N	N	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	N	9.5	35	92	0.8	P	N	N		N
N	Y	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	N	N	N	Y	N	11.8	12	104	0.8	N	N	N		Y
N	N	N	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	N	9.2	52	133	0.8	P	P	N		N
Y	Y	Y	Y	N	N	Y	Y	Y	N	N	Y	Y	N	N	N	N	N	14.2	9	156	0.8	N	N	N		Y
N	N	Y	N	N	Y	N	Y	Y	N	N	N	Y	N	N	N	N	N	9.2	38	79	0.6	P	P	N		N
N	N	N	N	N	Y	N	Y	N	N	N	Y	Y	N	N	N	N	N	8.9	25	80	0.8	P	N	P		Y
N	Y	Y	Y	N	N	N	Y	N	N	N	Y	Y	N	N	N	N	N	9.6	20	118	0.8	N	N	N		Y
N	N	N	N	Y	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	8.2	48	75	2.2	P	P	N		N
N	N	Y	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	10	35	52	0.8	P	P	N		N
N	Y	Y	Y	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	9.8	55	108	0.9	N	N	N		N
N	Y	N	N	Y	Y	N	N	Y	N	N	Y	Y	N	N	N	N	N	8.8	30	83	0.8	N	N	N		N
N	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	Y	N	N	N	N	N	10.2	40	60	1.2	P	N	N		Y
N	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	N	10.8	5	69	0.8	N	N	N		Y
N	N	N	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	Y	N	10.4	50	61	1.2	N	N	N		Y
N	Y	Y	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	8.2	5	71	0.8	P	P	N		Y
N	N	Y	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	8.6	100	82	0.8	P	N	P		N
N	Y	Y	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	13.6	36	88	0.9	P	P	N		Y
N	N	Y	N	N	Y	N	N	Y	N	N	Y	Y	N	N	N	N	N	9.8	24	128	1	N	N	N		N
N	Y	N	N	N	Y	Y	Y	Y	N	N	Y	Y	N	N	N	Y	N	10.4	74	114	0.8	P	P	N		Y
N	Y	Y	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	9	32	90	0.7	P	P	N		Y
N	N	Y	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	11.4	26	130	1.1	N	P	N		N
N	N	Y	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	13.2	20	108	0.9	P	N	N		N
N	Y	Y	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	N	N	8.8	42	114	0.8	P	N	P		Y
N	Y	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	N	Y	N	Y	N	9.2	38	104	1.1	N	P	N		Y

VOL.LOSS	pl.effusion	cardiomegaly	CT	CT-ground glass	reti nod	Honey Comb	Med LN	ILST	Nodules	broectasis	peribro th	pl effn	pl thickn	PFT	FVC	FEV1	FVC %	FEV1 %	FEV1/FVC	PFT	ECHO
Y	N	N		Y	N	Y	N	Y	Y	Y	N	N	Y		1.24	1.15	59	62	93	M.RESTRICTION	
Y	N	N		N	N	Y	N	Y	Y	Y	N	N	N		1.29	1.06	34	32	82.2	S.RESTRICTION	Alt,Sept,mo
Y	N	N		Y	Y	Y	N	Y	N	Y	N	N	Y		1.18	1.07	47	42	90.7	S.RESTRICTION	NORMAL
N	N	N		Y	Y	N	N	Y	Y	Y	N	N	N		1.66	1.55	52	56	93.4	M.RESTRICTION	NORMAL
N	N	N		N	N	N	N	N	N	N	N	N	N		4.41	4.17	103	114	94.6	NORMAL	NORMAL
N	N	N		Y	Y	Y	N	Y	N	N	N	N	N		1.5	1.35	69	74	90	M.RESTRICTION	NORMAL
Y	N	N		Y	Y	Y	N	Y	N	Y	N	N	N		1.02	1.02	40	47	100	S.RESTRICTION	NORMAL
N	N	N		Y	N	N	N	Y	N	N	N	N	Y		1.22	1.12	74	78	92	M.RESTRICTION	
N	N	N		N	N	N	N	N	N	N	N	N	N		1.91	1.83	60	76	95	M.RESTRICTION	NORMAL
N	N	N		Y	Y	Y	N	Y	Y	N	N	N	N		1.34	1.21	68	75	90	M.RESTRICTION	
N	N	N		N	N	N	N	N	N	N	N	N	N		2.21	1.78	96	92	81	NORMAL	NORMAL
N	Y	N		Y	Y	Y	Y	Y	N	Y	N	Y	Y		1.84	1.68	71	82	91	M.RESTRICTION	
N	N	N		N	N	N	N	N	N	N	N	N	N		2.58	0.38	74	12	14.7	S.OBSTRUCTION	NORMAL
Y	N	N		N	N	N	N	N	N	N	N	N	N		1.87	1.8	72	81	96.3	M.RESTRICTION	NORMAL
Y	N	N		Y	N	Y	N	N	N	Y	N	N	N		0.87	0.85	41	47	97.7	S.RESTRICTION	
N	N	Y		Y	N	N	N	N	N	N	N	Y	N		1.97	1.68	88	82	85	NORMAL	
N	N	N		N	N	N	N	N	N	N	N	N	N		2.34	1.87	82	84	80	NORMAL	
N	N	N		N	Y	N	N	Y	Y	Y	N	N	Y		1.13	1.13	66	81	100	M.RESTRICTION	NORMAL
N	N	N		N	N	N	N	N	N	N	N	N	N		1.66	1.46	86	90	87.9	NORMAL	NORMAL
N	N	N		Y	Y	N	N	Y	Y	N	N	N	Y		1.56	1.42	70	76	91	M.RESTRICTION	NORMAL
Y	N	N		Y	N	Y	N	Y	Y	Y	N	N	Y		0.97	0.87	35	37	89.7	S.RESTRICTION	
Y	N	N		Y	Y	Y	N	Y	Y	Y	N	N	Y		1.5	1.44	47	53	96	S.RESTRICTION	
N	N	N		Y	N	Y	N	Y	N	Y	N	N	Y		1.14	0.55	43	24	48.2	S.OBSTRUCTION	
N	N	N		N	N	N	N	N	N	N	N	N	N		1.94	1.82	75	81	93.8	NORMAL	NORMAL
Y	N	N		Y	Y	Y	N	Y	Y	Y	N	N	Y		1.66	1.36	69	68	82	M.RESTRICTION	NORMAL
N	N	N		Y	N	N	N	N	N	N	N	N	N		2.74	2.34	92	89	85	NORMAL	NORMAL
Y	N	N		Y	Y	Y	N	Y	Y	Y	N	N	Y		1.31	1.12	67	69	86	M.RESTRICTION	
N	N	N		Y	N	Y	Y	Y	N	Y	N	N	Y		1.42	1.23	72	76	86	M.RESTRICTION	
N	N	N		Y	N	Y	Y	N	Y	N	N	N	Y		1.33	1.24	59	70	93	M.RESTRICTION	NORMAL
N	N	N		N	N	N	N	N	N	N	N	N	N		2.45	2.24	85	97	91	NORMAL	NORMAL
Y	N	N		Y	Y	Y	N	Y	N	Y	N	N	Y		1.96	1.84	68	79	94	M.RESTRICTION	NORMAL
Y	N	N		Y	Y	Y	N	Y	Y	Y	N	N	Y		1.63	1.42	57	62	88	M.RESTRICTION	

LVEF	DIAS.DYSF	PAH	PSM	V.PERICAD	PERI.EFU	CHEMBER	AXIS	CAD	ARRYTHMIA	SEPT.INFAR	HEART BLOCK
51	Y	Y	Y	THICK	N	RVH	RAD	N	N	N	N
53	N	N	N	NORMAL	N	NORMAL	RAD	N	N	N	N
60	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
61	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
60	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
58	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
63	N	N	Y	NORMAL	N	NORMAL	NORMAL	N	N	N	N
58	N	N	N	NORMAL	N	NORMAL	RAD	N	N	N	LPHB
55	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
48	Y	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
58	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
54	N	N	N	NORMAL	Y	NORMAL	NORMAL	N	N	N	N
59	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
70	N	N	N	NORMAL	N	NORMAL	LAD	N	N	N	LAHB
60	Y	N	Y	NORMAL	N	NORMAL	NORMAL	N	N	N	N
59	Y	N	N	THICK	Y	LOW.VOL	NORMAL	N	N	N	N
52	Y	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
70	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
62	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
62	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
48	Y	Y	Y	THICK	N	RVH	LAD	N	N	N	RBBB+LAHB
50	Y	Y	Y	NORMAL	N	RVH	RAD	N	N	N	N
45	Y	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
60	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
63	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
58	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
49	Y	Y	Y	THICK	N	RVH	RAD	N	N	N	LPHB
58	Y	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
60	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	RBBB
63	N	N	N	NORMAL	N	NORMAL	LAD	N	N	N	LAHB
56	N	N	N	NORMAL	N	NORMAL	NORMAL	N	N	N	N
48	Y	Y	Y	NORMAL	N	RVH	RAD	N	N	N	N